EXAMINING THE EFFECTIVENESS OF MINDFULNESS MEDITATION

FOR CHRONIC PAIN MANAGEMENT IN COMBAT VETERANS

WITH TRAUMATIC BRAIN INJURY

By

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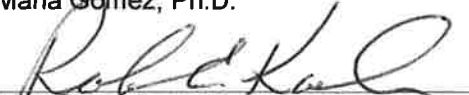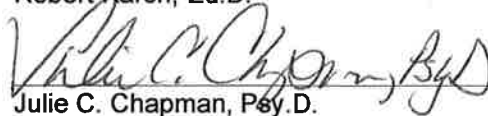
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ABSTRACT

One in three Americans suffer from chronic pain, a condition more prevalent and costly than heart disease, diabetes, and cancer. Patients and providers report dissatisfaction with standard medical care, prompting the need for further research on effective chronic pain treatments. This pilot study examined the effectiveness of mindfulness meditation (iRest®) for managing chronic pain in U.S. Veterans deployed to Afghanistan or Iraq. iRest is used clinically at Veterans Affairs (VA) hospitals nationwide. However, few studies have investigated the health benefits of iRest, and no study has examined this intervention's effectiveness for chronic pain. Veterans at the War Related Illness and Injury Study Center at the Washington, DC VA Medical Center were randomly assigned to receive iRest (n=4) or routine medical treatment (n=5) for 8 weeks. Self-reported pain intensity and interference was assessed at baseline (B), endpoint (E) and 4-week follow-up (F); patient ratings of improvement at E and F; and cognitive functioning and biochemical measures at B and E.

Veterans in the iRest group showed clinically meaningful reductions in pain intensity (23-42%) on the numeric rating scale and visual analog scale (VAS), and lowered pain interference (34-41%) on the Brief Pain Inventory and Defense and Veterans Pain Rating Scale. Effect sizes were large from B-E and B-F for pain interference (d=1.09–1.21) and medium to large for intensity (d=0.76–1.19). VAS pain intensity decreased from B-F $(p$=.041) and pain interference improved from B-E and B-F for both measures $(p$<.05). Among controls, no improvements in pain were detected, and changes were less than minimally significant (<20%). At E and F, iRest participants reported 'moderately better' to 'a definite improvement' in activity limitations, symptoms, and emotions related to their pain compared to 'hardly any change at all' among controls. From B-E, iRest participants improved in vigilance, the ability to sustain attention on the Conners' Continuous Performance Test II, compared to no difference among controls. Urinary cortisol and serum interleukin-6 remained unchanged from B-E in both groups. iRest is a

promising self-management approach for pain in Veterans. Further research is warranted to confirm its effectiveness as a viable treatment for chronic pain.

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INTRODUCTION

Pain is a universal experience intrinsically rooted in everyday existence. Human survival greatly depends on the unpleasant nature of pain, provoking individuals to avoid unnecessary injury or illness and to initiate behaviors that facilitate optimal health. Unrelenting pain, however, which endures for months or years after an injury has healed, no longer serves this vitally protective role. Pain that persists beyond 3 months, despite a resolved disease condition or physical injury to which the pain was initially related, is referred to as chronic pain (Merskey & Bogduk,1994).

One in three Americans suffer from chronic pain, a condition associated with profound psychological distress and diminished quality of life (Hardt et al., 2008; Johannes et al., 2010; National Center for Health Statistics, 2006; Portenoy et al., 2004). Pain is also the most frequent symptom for which patients seek medical care (Cherry et al., 2003; Kroenke, 2003). The number of U.S. adults with a chronic pain condition is approximately 100 million, surpassing the number of individuals with heart disease, diabetes, and cancer combined (IOM, 2011; Tsang et al., 2008). Compared to the annual domestic cost of heart disease ($309 billion), cancer ($243 billion) and diabetes ($188 billion), the financial burden of chronic pain conditions alone is estimated to be $560-$630 billion annually in health care expenditures and lost productivity, substantial enough to consider chronic pain a separate disease entity (Gaskin & Richard et al., 2012; IOM, 2011). The physical, mental, societal and economic issues surrounding this health concern support the need for continued research on chronic pain management, and to make these efforts a national health care priority.

The aim of this pilot study was to examine the effectiveness of mindfulness meditation for managing chronic pain in U.S. military Veterans who had sustained a traumatic brain injury (TBI) during deployment to Afghanistan or Iraq. Chronic pain is the most commonly diagnosed medical issue in this military cohort, (Kerns and Dobscha, 2009; Spelman et al., 2012), and is also highly co-morbid with TBI, PTSD and depression, adding complexity to the treatment of these health conditions. The specific type of mindfulness meditation used in this study, Integrative Restoration Yoga Nidra (iRest®), is used clinically at Veterans Affairs (VA) hospitals and military medical facilities nationwide. Additionally, iRest meditation is highly recommended for managing pain in military and Veteran populations according to the Army

Surgeon General's Pain Management Task Force, which cited Yoga Nidra as a Tier I intervention (Pain

Management Task Force, 2010). However, few studies have evaluated the effectiveness of mindfulness

meditation for chronic pain management and other comorbid health issues in Veteran populations (TBI,

PTSD, depression). This also represents the first study to research iRest specifically for managing chronic

pain.

<u>Chronic Pain in the U.S</u>.

Two important milestones in the past decade underscored the importance of chronic pain as a

mounting health care concern. In 2003, the U.S. Congress passed the National Pain Care Policy Act of

2003, declaring a "Decade of Pain Control and Research" (Kroenke et al. 2013). In 2011, the Institute of

Medicine (IOM) was mandated by the Department of Health and Human Services to produce a

comprehensive report to increase awareness of pain as a major public health problem in the U.S.

Findings from the IOM report emphasized the significant loss of physical and mental functioning, quality

of life, and productivity in those living with chronic pain (IOM, 2011). Pain conditions complicate medical

treatment for other illnesses, decrease worker productivity, and consequently account for the most

frequent reasons for physician visits, medication usage and work disability (Gaskin & Richard et al., 2012;

IOM, 2011). Of all chronic pain conditions, musculoskeletal joint and back pain are among the most

common, debilitating, and costly, having a significant functional and economic impact on working and

retired populations (IOM, 2011; Kroenke et al., 2013; Kroenke et al., 2003; National Research Council &

IOM, 2000). A meta-analysis of musculoskeletal pain studies by McBeth & Jones (2007) found that the

estimated prevalence of shoulder pain and back pain in the U.S. and abroad is 20-33% and 13-28%

respectively.

Chronic pain is widely recognized to be a major health concern among U.S. military Veteran

populations. In 1999, the Veterans Health Administration (VHA) implemented a national pain assessment

initiative at over 1,200 sites of medical care (VHA, 1999). "Pain as the 5th Vital Sign" required VHA health

care providers to measure and document patients' self-reported pain at all clinical encounters using the

numeric rating scale (NRS). Pain continues to be a significant health issue among the approximately 2.4

million service members that have been deployed to Afghanistan (OEF) and Iraq (OIF) since these

conflicts began in 2001 (Veterans Health Administration, 2011). Musculoskeletal pain conditions are the most frequently diagnosed medical issue in this military cohort, exceeding any other medical and psychological concern (Kerns and Dobscha, 2009; Spelman et al., 2012). A study of 91,000 OEF/OIF Veterans discharged from the military between 2001 and 2007 and receiving care from the Veterans Affairs (VA), found that 43% reported "any" pain; 63% of this subgroup (>25,000 Veterans) reported moderate to severe pain (Haskell et al., 2009). In a smaller sample of patients (n=793) seeking care at a Southwestern VA medical center, nearly 30% reported a level of pain that was clinically significant according to VHA pain guidelines ($\geq$ 4 on a numeric pain rating scale; Gironda et al., 2006). Clark (2002) found that 50% of a randomly selected sample of Veterans (n=300) in the general medical VA population exhibited at least one type of chronic pain. Collectively, these studies substantiate claims that OEF/OIF Veterans receiving care at Veterans Affairs (VA) hospitals report chronic pain more frequently than any other presenting complaint (Spelman et al., 2012; Clark, 2002).

<div align="center">

Comorbidity of Traumatic Brain Injury and Mental Health
Issues among U.S. Military Veterans

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Among military personnel who have served in the recent conflicts, traumatic brain injury (TBI) is considered the signature wound of OEF/OIF (Okie, 2005; Tanielian & Jaycox, 2008). An estimated 20% of troops may sustain a TBI as a result of a modern battlefield with improvised explosive devices (IEDs) (Tanielian & Jaycox, 2008). Additionally, battle wounds that in previous wars would have been fatal are now more treatable due to innovations in military medicine and body armor, enabling large numbers of seriously wounded soldiers to survive (President's Commission on Care for America's Returning Wounded Warriors, 2007; Warden, 2006).

Chronic pain is highly prevalent in combat Veterans who have sustained a TBI. Data pooled from 3 studies on Veterans who had sustained a TBI in theater (n=917) revealed that 43% of patients also reported chronic pain; this percentage rose to 75% in those with mild TBI (Nampiaparampil, 2008). Over-pressurization shock waves associated with high-order explosives are thought to represent the most common etiology of TBI in the current U.S. military conflicts in Iraq and Afghanistan (Warden, 2006). Current data suggest that TBI occurs in 50% of blast casualties (Stevenson, 2009). Compounding the effects of IEDs are vehicle-borne explosive devices and explosively formed penetrators (EFP); these

weapons have been increasingly implicated in blast injury both as a direct result of blast waves and due to secondary injury induced by flying debris (Hildreth, 2009). The prevalence of chronic pain and TBI, and the substantial overlap between them supports the need to investigate effective treatments and objective methods for determining treatment efficacy for patients living with these two health conditions.

The urban setting of the Iraq war, coupled with lengthy and repeated deployments to combat theater in both Afghanistan and Iraq, has made service members more vulnerable not only to physical injury, but also to intense, repeatedly occurring stressors (Gironda et al., 2006). Military deployment to a war zone may significantly alter health status and quality of life, elevating the risk of long-term physical, psychological, and social impairments (Spelman et al., 2012). Frequent exposures to high-explosive blasts, gunshot wounds, and motor vehicle accidents may explain the increasing number of persistent pain conditions and psychological issues seen among Veterans deployed to these combat areas (Clark, 2004). A cross-sectional study by Hoge et al. (2008) revealed that criteria for post-traumatic stress disorder (PTSD) were met in 44% of OEF/OIF soldiers with loss of consciousness and 27% of those with altered mental status, as compared to only 16% of soldiers with injuries other than TBI and 9% of uninjured soldiers. PTSD, TBI, and chronic pain tend to co-occur, adding complexity to the treatment of all three conditions simultaneously (IOM, 2011). In a study of 340 OEF/OIF Veterans at a VA Polytrauma Network site, 42% of patients exhibited co-morbid chronic pain, PTSD, and chronic postconcussive symptoms. According to the authors, "each of these conditions rarely occurs by itself"(Lew et al., 2009).

Depression is another commonly reported health issue in this military cohort. A telephone survey of 1,965 OEF/OIF military personnel deployed to OEF/OIF indicated that 14% met criteria for major depression, 14% screened positive for PTSD and 19% reported a deployment-related TBI (Tanielian & Jaycox, 2008). In another study of 289,000 OEF/OIF Veterans, Seal et al. (2009) showed that 36.9 % had a mental health diagnosis; of this number 21.8 % were diagnosed with PTSD and 17.4 % were diagnosed with depression (Seal et al., 2009). Pain is intimately related with psychological distress, particularly depression (Arnow et al., 2006; Bair et al. 2003; Fishbain et al., 1997) and anxiety (McWilliams & Goodwin, 2004).

Depression has been demonstrated to be especially prevalent in patients with chronic pain (Miller & Cano, 2009; Magni et al., 1993; Ohayon & Schatzberg, 2003) and in patients who have multiple

sources of somatic pain (Dworkin et al, 1990; Von Korff et al. 1988). A telephone interview study on a representative community sample of 1,179 participants showed that 35% of those individuals with chronic pain also had comorbid depression (Miller & Cano, 2009). Arnow et al. (2006) found that disabling chronic pain was a health issue in 41% of those with MDD compared to 10% of those without MDD in a population of 5,808 primary care patients. Several epidemiologic studies indicate a robust association between chronic pain and depression, however the causal relationship between these conditions remains inconclusive; chronic pain may trigger depression (Atkinson, Slater, Patterson, Gant, & Garfin, 1991), depression may cause chronic pain (Magni, Moreschi, Rigatti Luchini, & Merskey, 1994) or both conditions may be mutually reinforcing (Rudy, Kerns, & Turk, 1988). The robust association of pain with psychological distress prompts some clinicians to advocate depression and anxiety screening for patients with high self-reported pain intensity (Miller & Cano, 2009; Shelbourne et al., 2009). Even though depressive and anxiety symptoms tend to worsen as the severity of pain increases (Carroll et al. 2000; Moldin et al., 1993), interference of pain with everyday activities may be a stronger predictor of depression than pain intensity (Von Korff et al. 1992).

<u>Cognitive Impairment, Sleep Disturbance</u>
<u>and Fatigue</u>

In addition to musculoskeletal problems and mental health issues, other common health concerns seen in OEF/OIF veterans are medically unexplained symptoms which include fatigue, somatic complaints and impaired cognition such as memory, attention and concentration issues (Spelman et al., 2012). Research evidence has shown a convincing relationship between disrupted cognitive function and chronic pain in both patients and healthy individuals. Studies have found that chronic pain patients exhibit impaired performance on standardized everyday mental tasks (Dick & Rashiq, 2007; Dick et al., 2008). Berg et al. (2009) demonstrated that pain intensity was negatively correlated with speed of concentrated work and positively correlated with percentage of concentration errors. In another study, healthy participants subjected to task-irrelevant pain exhibited diminished performance on cognitive tasks, particularly in response to intense, novel, and threatening pain (Legrain et al., 2009).

Chronic physical pain conditions often lead to fatigue and sleep disturbances (Ohayon, 2005; Tuzun, 2007). Approximately 50–70% of chronic pain patients experience difficulty initiating and

maintaining sleep (Cohen et al., 2000; Atkinson et al., 1998; Morin et al., 1998). On the other hand, sleep quality and quantity can have a considerable impact on mental health, quality of life and overall physical functioning (Tuzun 2007; Ancoli-Israel, 2006; Manocchia et al., 2001), suggesting a reciprocal relationship between sleep disturbance and pain (Drewes & Arendt-Nielsen, 2001).

Depression may be a more significant contributor to sleep issues than pain. Among 201 Veteran outpatients at a VA pain clinic, depression predicted increased pain severity and sleep disturbance (Chapman et al., 2006). However, insomnia has been associated with elevated pain and distress in chronic pain patients, even when controlling for depression (Wilson et al., 2002). Collectively, pain, sleep disturbance and depression may be the most significant predictors of fatigue (Wolfe et al., 1996), which ultimately leads to difficulty managing everyday tasks, achieving optimal work capacity, and maintaining social relationships (Tuzun 2007). The causal relationship between pain and fatigue specifically has been supported by the scientific literature (Fishbain, 2003).

<u>Biomarkers of Chronic Pain</u>

Homeostatic factors play a significant role in chronic pain conditions. Musculoskeletal injury typically elicits a physiological response that attempts to establish equilibrium even after tissue healing has taken place. Stress is the primary consequence of homeostatic imbalance. Prolonged activation of the autonomic nervous system and the hypothalamic pituitary axis may elicit a feedback loop between pain and stress through the release of cortisol (Gatchel et al., 2007). The presence of stress-induced substances such as cortisol at sites of lesions and inflammation has been posited to comprise a neurosignature of pain (Melzack, 2005). Physical and psychological stress can also produce temporary increases in inflammatory cytokines such as Interleukin-6 (IL-6) (Kiecolt-Glaser et al., 2002; DeRijk et al. 1997, Zhou et al., 1993), which can directly act on pain pathways to cause hypersensitivity (Levine & Reichling, 1999; Raja et al., 1999).

Cortisol abnormalities may serve as a reliable biomarker of chronic pain (Tennant & Hermann, 2002). McBeth et al. (2005) reported that patients with chronic widespread pain and those exhibiting psychological risk for chronic pain were more likely to exhibit elevated serum cortisol compared to a reference group of individuals without pain or evidence of psychological distress. Additionally, dysfunction

of the HPA axis through high levels of serum cortisol has been shown to predict the eventual onset of chronic musculoskeletal pain in psychologically at-risk subjects (McBeth et al., 2007). Salivary cortisol (Anderson et al., 2008) and hair cortisol contents (Van Uum et al., 2008) were also found to be higher in chronic pelvic pain and severe chronic pain patients, respectively, when compared to healthy control subjects without chronic pain.

Serum cortisol abnormalities have been shown to be bidirectional in a number of chronic pain studies (Chapman et al., 1999; Glynn et al., 1978; Shenkin et al., 1964; Tennant et al., 2000). Severe pain may serve as a stressor that induces excess stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated serum cortisol concentration. Alternately, prolonged exposure to chronic pain and excess HPA stimulation may depress serum cortisol due to diminished adrenal reserve (Tennant & Hermann, 2002). In a population of patients with varied types of nonmalignant, chronic pain conditions, individual subjects predominantly exhibited either abnormally high or low serum cortisol concentrations. However, following successful opioid pain treatment, 73% of these patients exhibited a normalization of serum cortisol (Tennant & Hermann, 2002).

The divergent levels of HPA activation seen in chronic pain patients are also reflected in the two contrasting subtypes of major depression. Melancholic depression is characterized by hyperarousal of the HPA axis and resulting hypercortisolism, accompanied by anxiety, insomnia and loss of appetite (Gold & Chrousos, 2002; Gold, Goodwin, & Chrousos, 1988a; Gold, Goodwin, & Chrousos, 1988b). Atypical depression, on the other hand appears to involve a hypoactive HPA axis and abnormally low cortisol levels, complemented by lethargy, fatigue, hypersomnia and hyperphagia (Gold & Chrousos, 1999; Gold, Goodwin, & Chrousos, 1988a; Gold et al., 1996). The diminished cognitive and affective flexibility seen in major depression and stress disorders seem to be rooted in abnormal HPA activity (Gold & Chrousos, 2002; Gold & Chrousos, 1999; Gold, Kling, Whitfield et al., 1988).

Biomarkers of inflammation have also been implicated in the biochemical cascade of chronic pain. Several lines of evidence suggest that the proinflammatory cytokine IL-6 plays a vital role in the pathophysiology of pain. IL-6 production is dramatically elevated in peripheral nerves, dorsal root ganglia, and the spinal cord in humans in response to experimentally-induced pain (De Jongh et al., 2003). Furthermore, animal studies have shown that administration of IL-6 provokes pain by altering responses

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to painful stimuli, both thermal and mechanical. The injection of IL-6 in the rat hind paw induced dose-dependent sensitivity to mechanically-induced pain. Neutralizing IL-6 or altering the IL-6 pathway has also been shown to modulate pain perception. Inflammatory pain elicited by a carrageenan injection into the rat hind paw followed by local administration of anti-IL-6 antibodies resulted in lowered pain sensitivity (Cunha et al., 1992). Finally, clinical models demonstrate a significant correlation between pain intensity and gene expression of IL-6 at the site of inflammation, suggesting a prominent role of IL-6 in the pathophysiology of pain (Wang et al., 2009).

<p style="text-align:center">Current Treatment Approaches for Chronic Pain</p>

Despite efforts by the IOM, VHA, and U.S. Congress to generate public awareness of chronic pain as a universal health problem, chronic pain is widely undertreated in a variety of settings (Cleeland et al., 1994; Green et al., 2001; Matthias et al., 2010b; Zhukovsky et al., 1995). Since specialized pain clinics are not readily available in a number of health care settings, chronic pain is often treated in primary care (Matthias et al., 2010b). Barriers to providing effective treatment in primary care clinics include lack of pain management training and consensus on optimal treatments, time constraints, and concerns regarding the use of opioids for chronic noncancer pain (Bendtsen et al., 1999; Eriksen et al., 2006; Turk et al., 1994).

In the U.S. pain medications are the second most frequently prescribed class of drugs (Turk, 2002), yet analgesics fall short of providing adequate relief in many patients (Curatolo & Bogduk, 2001; Von Korff et al., 2011). Additionally, clinicians have often expressed concerns about potential misuse of opioid pain medications and regulatory scrutiny (Green et al., 2001; Weinstein et al., 2000; Potter et al., 2001; Nedeljkovic et al., 2002). In a study of 45 clinicians working in five primary care clinics at a VA medical center, 40% of clinicians felt that their concerns with contributing to opioid dependence influences their management of chronic pain, and 20% reported that patients became addicted in more than half of the cases when opioids were prescribed for chronic pain (Dobscha et al. 2008). Nonetheless, chronic pain patients are routinely treated with opioid medications (Koch, 1986; Turk & Okifuji, 2002), and medical use of opioids has risen dramatically over the last decade (Joranson et al., 2000; Turk, 2002; Mitka, 2003; Clark, 2002).

Patients and providers both report dissatisfaction with the procedures and outcomes of standard chronic pain care and medical treatments (Clark & Upshur, 2007; Green et al., 2001; Potter et al., 2001; Upshur et al., 2006). Dobscha et al. (2008) determined that 71% of VA clinicians felt confident in their abilities to treat chronic pain, and 77% concurred that skilled pain management represents a high priority. However, 73% agreed that patients with chronic pain represent a significant source of frustration and 38% reported dissatisfaction with their ability to deliver optimal pain treatment. Another study revealed similar issues and concerns among VA primary care providers in regards to their chronic pain patients, such as feeling compelled to treat with opioids, uncertain about the credibility of patient reports of pain, and the emotional toll they face as providers in chronic pain care (Mathias et al., 2010b). Patients, on the other hand, have described their experience with primary care providers as not being understood or listened to, rarely obtaining sufficient pain medication, and having limited treatment options beyond medication (Bair et al., 2009; Matthias et al., 2010a; Upshur at al., 2010). Collectively, these results suggest that health care providers and patients alike may benefit from effective treatment alternatives to assist both parties in more effectively and satisfactorily treating pain (Dobscha et al. 2008).

A Cultural Transformation in Chronic Pain Care

Because chronic pain encompasses cognitive and emotional factors, in addition to the biological factors that pain medications seek to address, IOM argues that this complex interrelationship appeals for a "cultural transformation in the way pain is understood, assessed, and treated" (IOM, 2011). Pain medicine within the VHA is on the frontier of addressing chronic illness from a biopsychosocial perspective (Gallagher, 2009).

The biopsychosocial model focuses on the complex interplay between biological, psychological, and social factors. Because musculoskeletal injury involves the stimulation of nerves that carry nociceptive information about potential tissue damage to the brain, pain is the subjective perception that results from interpreting this incoming sensory information. This input is typically modulated by an individual's genetic make-up, prior experiences, psychological state, and sociocultural factors. Psychosocial factors such as emotions provide an immediate reaction to nociception, whereas cognitions attach meaning to the emotional response; if the cognitions elicit other emotional reactions that

exacerbate the pain experience, a vicious cycle of nociception, pain, distress, and disability may be perpetuated. Although sensory mechanisms of pain have been historically given the most attention, cognitive, affective and behavioral factors are becoming increasingly central to understanding chronic pain and developing effective treatments (Gatchel et al., 2007).

The complexity of chronic pain urges providers to individualize pain care to each patient's experience and to encourage self-management, a recent health care practice that emerged from the Chronic Care Model (Mathias et al., 2012b; Wagner, Austin, & Von, 1996). This model was derived from effective interventions to improve outcomes among patients who require sustained treatment management as opposed to episodic acute care (Upshur et al., 2010). Patient-centered care offers a similar model, in which patients are empowered and treated as partners in their health care (Mead et al., 2000; Stewart et al., 1995).

Self-management was recognized by the VHA and IOM as a channel through which patients may take an active role in managing and coping with pain (IOM, 2003). Self-management has been defined as "the ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition" (Barlow et al., 2002). Since chronic pain patients must live with and manage pain daily, self-management is an essential component of effective pain treatment. Self-management programs have been demonstrated to be effective in managing chronic pain. A meta-analysis by Warsi et al. (2003) showed that self-management programs resulted in modest but statistically significant reductions in pain and disability.

Self-management programs foster patient self-efficacy by enabling individuals with chronic pain to acquire cognitive, behavioral, and emotional techniques and skills to establish a satisfactory quality of life (Barlow et al., 2002; Matthias et al., 2012a). Self- interventions encourage patient involvement and control, in addition to improving their understanding of how their condition and treatment influences their lives (Matthias et al., 2010a). Through this process, patients can develop a sense of empowerment and a belief they can control their experience of pain under many circumstances (Keefe et al., 2008).

Mindfulness Meditation and Chronic Pain

Mindfulness meditation has great potential to improve health outcomes and quality of life among military service members and Veterans. Because mindfulness meditation may be practiced independently after learning the techniques through structured classes, it is a sustainable, economically viable intervention that can be used to treat chronic pain as an alternative or adjunct to standard medical care in Veteran and military health settings (Cuellar et al., 2008). Mindfulness-based meditation practices offer the largest body of research evidence amongst different relaxation techniques for pain, according to a meta-analysis conducted by Army Colonel Rees (2011). Pain relief in OEF/OIF Veterans with musculoskeletal injury may be achieved through strategies that manage stress and achieve deep relaxation such as meditation, which has been found to improve pain outcomes in a number of populations (Spelman et al., 2012).

Studies have demonstrated that mindfulness practice decreases self-reported pain in response to experimentally induced stimuli in healthy individuals. Kingston et al. (2007) found that 6 hours of mindfulness meditation training resulted in heightened pain tolerance on the cold pressor test in comparison to a control group exposed to guided imagery. Zeidan, Gordon, Merchant, & Goolkasian (2010) showed that 3 days of mindfulness meditation training resulted in lowered pain sensitivity to pain in response to electrical stimuli. Grant & Rainville (2009) applied thermal stimuli to the calf of experienced Zen meditators versus meditation-naïve controls to discover that significantly higher temperatures were needed to induce moderate pain in meditators practicing mindfulness compared to control subjects. Reported pain intensity among meditators was significantly lower than controls, and those with the most meditation experience showed the largest reductions.

Pain sensitivity may also be associated with changes in brain activity and structure in pain-related neural regions. Four days of mindfulness training in healthy volunteers produced reductions in pain intensity and pain unpleasantness of 40% and 57%, respectively while meditating compared to a rest condition in response to noxious thermal stimuli (Zeidan et al. 2011). Notably, these meditation-induced decreases in pain intensity were correlated with increased brain activity in the anterior cingulate cortex and anterior insula, structures implicated in cognitive regulation of nociceptive processing (Zeidan et al. 2011). Grant et al. (2010) demonstrated that cortical thickness in pain-related brain regions such as the

cingulate cortex was not only greater in experienced Zen meditators versus controls, but was also positively correlated with number of years of meditation experience and decreased pain sensitivity to thermal stimuli.

Meditation has also been shown to influence biomarkers of stress in chronic pain patients and health individuals. Kiran et al (2005) reported a significant reduction in pain severity in chronic tension headache patients receiving 2 weeks of meditation compared to no change among patients prescribed Alprazolam. These findings were accompanied by increased normalization of plasma cortisol levels among meditators versus no significant change in abnormal cortisol levels among patients receiving drug treatment (Kiran et al., 2005). Additionally, Tang et al (2010) demonstrated that healthy individuals exposed to 5 days of meditation practice exhibited a lowered cortisol response to mental stress as compared to a control group.

A growing body of research suggests that mindfulness meditation may play a role in reducing physical symptom complaints and improving emotional functioning in chronic pain patients (Rosenzweig et al., 2010). Increased mindfulness is correlated with lower ratings of pain intensity in chronic pain populations (Carmody & Baer 2008; McCracken et al., 2007; McCracken & Thompson, 2009). A study employing mindfulness meditation techniques (guided imagery and progressive muscle relaxation) to novice meditators demonstrated significant decreases in reported pain among patients with chronic osteoarthritis compared to no change in the control group (Baird et al., 2004). Plews-Ogan et al. (2005), on the other hand, found no significant difference in reported pain sensation or unpleasantness in chronic musculoskeletal pain patients receiving mindfulness, however mental health status improved (Plews-Ogan et al., 2005). A meta-analysis by Veehof et al. (2011) on the effectiveness of acceptance-based therapies on mental and physical health in chronic pain patients found medium pre to post treatment effect sizes for pain intensity, depression, anxiety, physical wellbeing and quality of life. Reiner et al. (2013) determined that among 8 controlled studies included in his meta-analysis, 6 studies reported significantly greater reductions in pain intensity for the mindfulness-based intervention group (ranging from 11.8% to 49.4%) as compared to controls. Most studies described in these meta-analyses employed pain intensity as a primary outcome measure. However, Veehof et al. contends that pain intensity may not be the most appropriate means to assess these interventions, since decreasing pain intensity is not a principal focus of acceptance-based therapies. Because mindfulness practices teach students to let go of

pain control strategies and practice acceptance of pain as a part of daily life, larger effect sizes for pain

intensity may not be likely (Veehof et al., 2011). Future studies, according to Veehof et al. should not rely

exclusively on pain intensity but also include other outcome measures such as interference of pain with

daily life.

<u>Mindfulness Meditation and Cognitive Functioning</u>

The experience of pain can place appreciable demands on attentional resources, such that an

activity or cognitive task may require abrupt shifts of attention between the primary task and pain

sensation (Eccleston & Crombez, 1999; Elomaa et al., 2009). This increased attentional focus on pain

may lead to recurring interruptions and subsequent disruption of ongoing activities (Eccleston and

Crombez, 2007). In cases where chronic pain adversely impacts attentional focus, successful treatment

of pain would be expected to improve cognitive functioning. As an attention management technique,

mindfulness meditation fosters increased mental focus, which may help patients begin to address the

disabling effects of chronic pain. Mindfulness interventions have been shown to improve attentional

functioning and reduce emotional disturbance in individuals with persistent pain (McCracken et al., 2007).

Several lines of evidence illustrate that mindfulness training may enhance the ability to maintain

focus on task-relevant information, and concurrently enable the individual to filter out distracting or

irrelevant stimuli (Stanley & Jha, 2009). Improved cognitive performance (Cahn & Polich, 2006) and

enhanced attentional processes (Jha, Krompinger, & Baime, 2007; Slagter et al., 2007) have been

demonstrated in healthy individuals who have undergone extensive meditation training. Lutz et al. (2009)

found that 3 months of intensive meditation training improved sustained attention and reaction time during

a dichotic listening task. Buddhist meditators have exhibited superior performance on cognitive tests of

sustained focused attention compared to controls of comparable educational level (Valentine & Sweet,

1999). Higher levels of self-reported mindfulness in Buddhist meditators were also associated with

sustained attention (Moore & Malinowski, 2009). A neuroimaging study by Short et al. (2007) showed that

meditation training increased activation in executive attention networks correlated with sustained attention

and error monitoring improvements. Finally, Zeidan, Johnson, Diamond, David, & Goolkasian et al. (2010)

showed that healthy college students randomized to 4 days of mindfulness meditation performed better

on cognitive tasks requiring sustained attention and executive processing efficiency compared to those assigned to a book listening group. Although these studies were focused on civilian populations, the findings are especially relevant to military and Veteran settings. Mindfulness techniques could help optimize everyday performance by developing proficiencies essential for activities on and off the battlefield, such as enhanced self-regulation, improved attentional skills, and heightened situational awareness (Stanley & Jha, 2009).

<u>Research on iRest Yoga Nidra</u>

A literature review on iRest, the specific form of mindfulness meditation currently being researched, reveals a handful of studies focused on college students and counselors, and patients with chronic health conditions, including multiple sclerosis, cancer, and PTSD. Undergraduate and graduate students enrolled in 8 weeks of iRest showed significant reductions in perceived stress, worry and depression accompanied by increases in mindfulness. Qualitative data retrieved from individual student participants provided evidence for increased coping and relaxation skills in addition to heightened self-awareness (Wilson, Eastman-Mueller, & Jung, 2008). Birdsall, et al. (2011) found that iRest practice resulted in significant decreases in perceived stress and fatigue in college counselors. However, no differences were observed in vigor, anger, tension, confusion, and depression. In a study on female college students randomly assigned to three different interventions, the group receiving iRest scored significantly higher on positive affect post-intervention compared to participants in the relaxation response meditation or audio book conditions. Additionally, a decreasing trend in salivary cortisol was found in iRest participants, compared to no change in the relaxation response meditation group and significantly higher cortisol levels in the audio book group (Borchardt, Patterson, & Seng 2012). Homeless adults receiving brief training in iRest demonstrated lowered perceived stress and psychological distress in addition to enhanced quality of life (Bhogaonker, 2012). A study involving multiple sclerosis patients and cancer patients showed significantly reduced stress scores in both patient groups after six iRest sessions (Pritchard, Elison-Bowers, & Birdsall, 2009).

Two studies have been conducted on iRest in active-duty military and Veteran populations with PTSD, however neither employed a control group. In the first study, military patients at Walter Reed Army Medical Center showed a decreasing trend in self-reported PTSD symptoms in response to 9 weeks of iRest (Engel). Stankovic (2011) researched the feasibility of an 8-week iRest program for Vietnam-era male combat Veterans. iRest practice led to decreased emotional reactivity, improved regulation of rage and anxiety, and heightened feelings of relaxation, peace, self-awareness and self-efficacy.

<u>Study Overview</u>

This study aims to evaluate the effectiveness of mindfulness meditation for chronic pain management in a population of Veterans previously deployed to OEF or OIF who have sustained a TBI. The form of meditation employed in this study (iRest) was developed by Dr. Richard Miller, clinical psychologist, founder and executive director of the Integrative Restoration Institute. This mindfulness meditation practice was designed to promote deep relaxation through breathing, guided imagery, progressive relaxation and body sensing techniques. iRest is a commonly used intervention in clinical settings nationwide including VHA medical centers at Washington DC, Miami, Chicago, Sacramento and Palo Alto, in addition to active duty military facilities at Walter Reed, Fort Belvoir and Brooke Army Medical Centers. However, few studies have researched the health benefits of iRest to confirm the effectiveness that Veterans routinely report, and no study to our knowledge has examined the utility of iRest for chronic pain in particular.

The current study was conducted at the War Related Illness and Injury Study Center at the Washington, DC VA Medical Center (WRIISC-DC). iRest is currently provided to Veterans in one-hour sessions, twice per week as part of the Integrative Healthcare and Wellness Program in the WRIISC-DC. The purpose of this study was to validate the potential health benefits of this meditation program, which Veterans reported after participating in the iRest program. Surveys completed by 184 Veterans at the WRIISC-DC revealed that their pain-related symptoms improved after participating in the iRest program. Among the most significant findings, Veterans indicated improvements in sleep (81%), musculoskeletal pain (76%), back pain (72%), and headaches (51%; Reinhard et al., 2012). The central goal of this pilot study was to examine whether iRest, as an adjunctive therapy to standard medical care, relieves chronic

pain more effectively than standard care alone. The aforementioned literature review of mindfulness meditation studies provides convincing evidence for the potential health benefits of this intervention for chronic pain and related health issues. Therefore, it is hypothesized that iRest practice will result in significantly greater improvements in pain and accompanying comorbidities (PTSD and depressive symptoms, cognitive impairments, cortisol and IL-6 abnormalities) as compared to Veterans receiving standard medical care alone.

CHAPTER 2

METHODS

<u>Participants</u>

Study participants were recruited at the Washington, DC Veterans Affairs Medical Center (DC VAMC). Institutional Review Board (IRB) and Research & Development (R&D) Committee approval was granted by the DC VAMC and American University. All participants provided written informed consent for the pre-study screening and the 8-week study. Contact information for the Principal Investigator was provided to participants for study-related questions.

Inclusion criteria included 20 to 60 years of age, male, military deployment to OEF or OIF, current enrollment at the DC VAMC, and mild or moderate TBI. Exclusion criteria consisted of 1) alcohol consumption > 3oz/day or illicit substance use within the past month, 2) prescription medication use that could influence self-reported pain, cortisol, or IL-6 measures (analgesics other than NSAIDS, antipsychotics, tricyclic antidepressants, or glucocorticoids), and 3) attending more than four meditation sessions in the past 6 months.

An initial phone screening based on these inclusion/exclusion criteria was conducted to determine eligibility for the pre-study screening. Eligible participants were consented for the pre-study and asked to report their pain intensity within 1 hour of waking for 3 days in one week (Monday, Wednesday, Friday). A numeric rating scale (NRS) was used for this pre-study screening with the following language: 'On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain right now?' The purpose of this screening was to ensure that patients had an adequate level of pain before being admitted to the study. Subjects with an average reported pain rating $\geq$ 5 out of 10 were eligible to participate in and were consented for the 8-week study.

Figure 1 provides a study flowchart for recruitment, screenings, and group assignment. Recruitment flyers were mailed to 838 OEF/OIF Veterans who had visited the DC VAMC in the past 6 months. Flyers were also distributed to Veteran outpatients and health care providers in the WRIISC, Polytrauma, Neurology, Trauma Services, and Primary Care clinics at the DC VAMC. A total of 118 patients expressed initial interest in the study. Of these participants, 43 were unable or unwilling to participate (time commitment, work schedule, transportation to the DC VAMC, physical mobility), 51 did

not meet eligibility criteria for the initial phone screening, and 24 were eligible for the pre-study screening. Reasons for ineligibility included patients who were not deployed to OEF/OIF, did not sustain a brain injury, or were taking prescription medications that would influence outcome measures. All 24 eligible Veterans were consented and enrolled in the 1-week pain screening. Of this group, three did not complete the pain screening, six were not eligible (pain rating $\leq$ 5), and two could not be reached for scheduling. The remaining 13 Veterans were consented, enrolled, and randomly assigned to receive either 8 weeks of iRest (case group) or treatment as usual (control group). To ensure allocation concealment, an investigator not involved in recruitment, group assignment or treatment generated the allocation sequence. Block randomization was employed using a 2:1 allocation ratio (case group: control group) and a block size of three to facilitate initiation of the iRest group sessions with an adequate number of case group participants.

Ten patients completed the study and the follow-up measures. Attrition occurred exclusively in the case group. Two participants dropped out of the study due to the time commitment, according to oral accounts; one patient stopped attending study sessions at the DC VAMC and could not be reached by the researchers. Finally, 1 participant was excluded from the data analysis to avoid potential confounds; this patient experienced a fall (outside of the DC VAMC) that resulted in a loss of consciousness and probable TBI during the study. In total, 4 case and 5 control group participants were included in the final analysis.
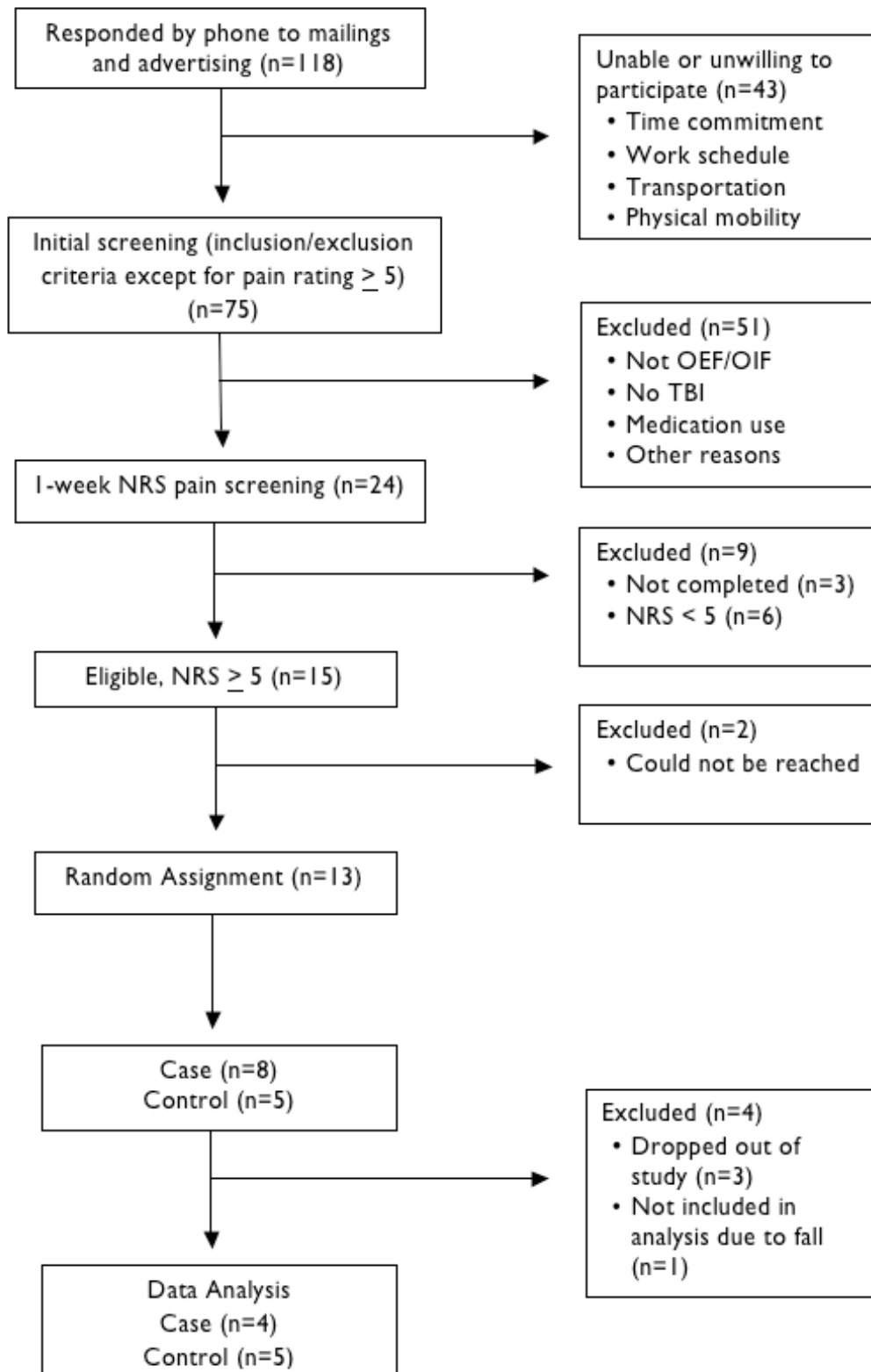
Figure 1. Flowchart for Recruitment, Screenings, and Group Assignment.

Intervention

The 8-week iRest program consisted of two 1-hour sessions per week at the DC VAMC. To standardize instruction, both iRest classes were led by the same instructor who received her iRest training from the Integrative Restoration Institute (IRI). An additional make-up session was offered each week to participants who missed one of the regularly scheduled classes; this make-up session was taught by a different instructor who was also trained by IRI. The participants were offered three formal iRest sessions per week and were expected to attend at least two of these sessions. Comments made by individual participants about their practice of iRest were recorded by the instructor throughout the study to obtain qualitative data. To further immerse Veterans in the iRest intervention, participants were encouraged to self-administer iRest daily by listening to audio recordings outside of the formal sessions at the DC VAMC. The audio recordings utilized the same instructor providing the same practice as the formal sessions at the DC VAMC. To facilitate the goal of daily practice, each case group patient was provided an iPod with three iRest audio exercises and an iRest workbook (An Introduction to Integrative Restoration: iRest® Yoga Nidra). Patients were asked to fill out a self-practice log to document the time of day and describe their overall experience after each self-practice session. Upon completion of the study, case group participants were permitted to keep the iPod and workbook to continue their personal self-practice of iRest. At the end of the study, control group patients were provided all study materials (iRest workbook, iPod with audio exercises) and access to iRest sessions at the DC VAMC. Patients from both groups continued to receive their usual medical care throughout the study period. At study end, all participants were compensated $20 to help defray travel expenses.

Measures

Because chronic pain is often associated with an array of concomitant symptoms such as psychological distress, functional impairment, and disability (Hardt et al., 2008), meaningful evaluation necessitates the administration of multi-dimensional subjective measures and health-related quality of life instruments (Breivik et al., 2008). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) identified four outcome domains for the assessment of pain in clinical trials: pain intensity, physical functioning, emotional functioning and patient rating of improvement (Dworkin et

al., 2008). Table 1 aligns each IMMPACT outcome domain with the self-report measures employed in this study. Additionally, the World Health Organization Quality of Life – BREF (WHOQOL-BREF), relevant to both physical and emotional functioning domains, was used to assess overall health-related quality of life. Because chronic pain assessment should also take into account cognitive impairment (Breivik et al., 2008), cognitive functioning was measured using Conners' Continuous Performance Test (CPT-II). Since qualitative examination of patients' experiences is critically important when researching chronic pain interventions (Mathias et al., 2012b), study participants were provided a self-practice log to describe their overall experience after iRest sessions.

Table 1.

IMMPACT Core Outcome Domains for Pain Assessment and Associated Self-report Outcome Measures Employed in this Study

Domain	Measure
Pain Intensity	Visual Analog Scale (VAS)
	Brief Pain Inventory (BPI)—pain severity subscale
	Defense and Veterans Pain Rating Scale (DVPRS)—NRS
Physical Functioning	BPI—pain interference subscale
	DVPRS—pain interference subscale
Emotional Functioning	Beck Depression Inventory (BDI)
	Affective Control Scale (ACS)
	PTSD Checklist—Military Version (PCL-M)
	Five Facet Mindfulness Questionnaire (FFMQ)
Patient Rating of Improvement	Patient Global Impression of Change (PGIC)

Finally, quantitative measures of urinary cortisol and serum IL-6 were employed to determine if changes in self-reported pain intensity and emotional functioning are associated with biochemical measures of stress and inflammation. This multimodal assessment approach was employed in the study design to comprehensively examine the effectiveness of iRest for managing chronic pain and other associated comorbidities.

A description of each measure employed in the study design is provided below.

Pain Intensity/Physical Functioning:

- Visual Analog Scale (VAS) is a measure of pain intensity in which patients rate their level of pain 'right now' by drawing a mark on a 10-cm line from 'no pain' (0 mm) to 'worst pain imaginable' (100 mm).

- Brief Pain Inventory (BPI) assesses pain intensity (referred to as "pain severity") and the interference of pain in daily life (called "pain interference"), both using numeric rating scales from 0 to 10. The 4-item severity subscale includes 1) 'pain at its worst in the last 24 hours' and 2) 'pain at its least' in the last 24 hours, 3) 'pain on average' and 4) pain 'right now.' The 7-item interference subscale assesses the extent pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life during the past 24 hours from 0 'does not interfere' to 10 'completely interferes' (Cleeland & Ryan, 1994). The numbers for each subscale are averaged together to yield a mean value for pain "severity" and "interference" for each patient.

- Defense and Veterans Pain Rating Scale (DVPRS) was developed by the Army Pain Management Task Force to evaluate pain intensity and pain interference in military and Veteran populations. The pain intensity scale is an enhanced version of the NRS that includes visual cues and verbal descriptors to improve interpretability of incremental pain intensity levels. These enhancements include descriptors for each pain level (i.e. 0 = 'no pain,' 5 = 'interrupts pleasurable activities,'10 = 'excruciating, nothing else matters'), color gradients to indicate pain severity (green=mild, yellow=moderate, red=severe) and facial expressions to illustrate perceived pain. The 4-item interference subscale assesses pain interference with general activity, sleep, mood, and stress in the last 24 hours from 0 'does not interfere' to 10 'completely interferes'

(Buckenmaier et al., 2013). The numbers for the interference subscale are averaged together to yield a mean value for pain "interference" for each patient.

Emotional Functioning:

- Affective Control Scale (ACS) is a 42-item scale assessing fear of strong emotions and ability to regulate emotional experience (Williams et al., 1997).

- Beck Depression Inventory-II (BDI-II) is a widely used 21-question self-report measure of depressive symptomatology (Beck et al., 1996).

- Five-Facet Mindfulness Questionnaire (FFMQ) is a 39-item measure of five factors: observing, describing, acting with awareness, accepting without judgment, and non-reactivity to inner experience. The FFMQ measures participants' ability to be mindful in daily life (Baer et al., 2006).

- PTSD Checklist—Military Version (PCL-M) is a 17-item self-administered questionnaire used to assess post-traumatic stress disorder (PTSD) for military personnel and Veterans. It is based on DSM-IV criteria for the three symptom clusters of PTSD: re-experiencing, numbing/avoidance, and hyper-arousal. Each item asks how much an individual has been bothered by a particular symptom in the past month using a 5-point scale, from 1 'Not at all' to 5 'Extremely' (Weathers et al., 1993).

Patient Improvement:

- Patient Global Impression of Change (PGIC) consists of a 7-item scale, an 11-point NRS, and a list of common symptoms. The 7-item scale prompts subjects to "describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life related to your painful condition" since beginning this study by selecting the appropriate description on a 7-item scale, from 1 'no change or condition has got worse' to 7 'a considerable improvement that has made all the difference.' The 11-point NRS evaluates the "degree of change since beginning this study" from 0 'much better' and 5 'no change' to 10 'much worse'. Subjects are then provided a list of symptoms and asked if they "noticed any improvements in the following symptoms since beginning this study: back pain, musculoskeletal pain, headaches, upset stomach, constipation/diarrhea, trouble sleeping, energy level, irritability/angry outbursts, concentration,

depression, and anxiety." Possible choices include 'yes completely', 'yes somewhat', 'no' and 'don't have this problem.'

Cognitive Functioning:

- Conners' Continuous Performance Test II Version 5 (CPT II) is a computerized test of attention lasting 14 minutes in duration. The test presents targets and non-targets over the course of 18 blocks. Subjects are instructed to press a button as quickly as possible every time the target letter appears. CPT II results may be used to assess inattention, impulsivity, and vigilance (Conners & MHS, 2004).

Health-Related Quality of Life:

- World Health Organization Quality of Life – BREF (WHOQOL-BREF) is a 26-item instrument that evaluates satisfaction with physical health, everyday life, social relationships, and environment (WHO, 1993).

Procedures

Self-report, cognitive functioning and quantitative measures of neuroendocrine (cortisol) and immune (IL-6) function were administered at specified study time points: baseline (week 0), midpoint (end of week 4), endpoint (end of week 8), and follow-up (end of week 12). Table 2 provides the timeline of administration for each study measure.

A Health and Demographics Questionnaire designed by the researchers was administered at baseline. A medical pain specialist at the DC VAMC conducted the Clinical Pain Evaluation to determine the specific type, location, and relative intensity of pain experienced by each patient (i.e. musculoskeletal vs. neuropathic, lower back vs. head pain) at baseline. The Clinical Pain Evaluation was repeated at endpoint to evaluate patient-reported improvement or worsening of each pain area from baseline. The medical pain specialist was blind to group assignment. Self-report measures of pain intensity/physical functioning (VAS, DVPRS, BPI) and emotional functioning (BDI-II, PCL-M, ACS, FFMQ) were administered at baseline, midpoint, endpoint, and follow-up. Patient improvement (PGIC) was evaluated at midpoint, endpoint, and follow-up. Quality of life (WHQOL-BREF) and cognitive functioning (CPT II)

were assessed at baseline and endpoint. The CPT II was administered on an HP Elite Book 8560w

laptop computer with the Conners' Continuous Performance Test II Version 5 software installed.

At baseline and endpoint, one blood sample (5mL) was collected from each participant by a phlebotomist

in the DC VAMC out-patient lab and stored in a gold top tube. After 20-30 minutes to allow for

coagulation, each sample was centrifuged at 4480 RPM (3600 Gs) for 10 minutes to obtain approximately

2.5 mL of serum. Each sample was aliquoted into two 2mL cryotubes and stored in a -80 degree

Fahrenheit freezer until the end of the study.

Table 2

Timeline of Study Measure Administration

Baseline	Midpoint	Endpoint	Follow-up
Week 0	End of Week 4	End of Week 8	End of Week 12
VAS	VAS	VAS	VAS
DVPRS	DVPRS	DVPRS	DVPRS
BPI	BPI	BPI	BPI
BDI-II	BDI-II	BDI-II	BDI-II
ACS	ACS	ACS	ACS
FFMQ	FFMQ	FFMQ	FFMQ
PCL-M	PCL-M	PCL-M	PCL-M
HDQ	PGIC	PGIC	PGIC
WHOQOL		WHOQOL	
CPT II		CPT II	
Clinical Pain Evaluation		Clinical Pain Evaluation	
Urine collection (cortisol)		Urine collection (cortisol)	
Blood draw (serum IL-6)		Blood draw (serum IL-6)	

Note. HDQ=Health and Demographics Questionnaire. WHOQOL= WHOQOL-BREF.

Serum IL-6 was measured using Quantikine HS Human IL-6 Immunoassay; R&D Systems, Inc., Minneapolis, MN, USA. The sensitivity of the IL-6 assay is 0.039 pg/ml with inter- and intra-assay coefficients of variability of approximately 8% and 7%, respectively. At baseline and endpoint, each participant collected a 24-hour urine specimen as an out-patient and returned the sample to the DC VAMC Core Lab. Urinary free cortisol (UFC) was measured by liquid chromatography and tandem mass spectrometry by Quest Diagnostics. Urinary cortisol excretion (micrograms/24 hours) was expressed per concomitant daily urinary creatinine excretion (grams/24 hours).

Statistical Analyses

A power analysis was calculated to determine the sample size required to detect a clinically significant reduction in chronic pain on the numeric rating scale (NRS). The analysis was based upon a mindfulness intervention study on chronic pain patients (MacIver et al., 2008). Because of the similarities between iRest and the interventions employed in the MacIver study (body sensing and meditation), it was deemed to be an appropriate study for sample size calculation. Russ Length's Power and Sample Size webpage (University of Iowa, 2006) was utilized. A one-sample paired t-test (alpha=.05, sigma=2.3) with a difference of means=3.4 (MacIver et al. 2008) determined that a sample size of n=7 participants for the experimental group would be sufficient to achieve a power=0.9. A statistically significant reduction in pain will be defined as a 20% reduction on the NRS, which IMMPACT recognizes as a minimally important change in chronic pain intensity (Dworkin et al., 2008). Moderately and substantially important changes are equated with 30% and 50% reductions in pain, respectively.

The Shapiro-Wilk test was performed to assess for normality of case (n=4) and control (n=5) group data for each measure. Q-Q plots were inspected for normality and nearly every measure was normally distributed according to the Shapiro-Wilk test (p>.05) except for BPI severity at endpoint (p<0.5). Baseline characteristics between case and control groups were compared using two-tailed independent samples *t*-tests. Because 2 participants did not complete midpoint measures, only baseline, endpoint, and follow-up data were analyzed. Change in continuous dependent variables was assessed over two time intervals: 1) from baseline to endpoint and 2) from baseline to follow-up). Two-factor mixed ANOVA served as the initial analysis, consisting of a between-subjects factor with 2 levels (case, control) and a

within-subjects factor with 2 levels (baseline, endpoint or baseline, follow-up). Paired *t*-tests were

conducted as a secondary analysis to compare pre (baseline) vs. post (endpoint or follow-up) measures

within each group (case, control). Although assumption violations may be difficult to detect in small

sample sizes (BBN, 1996), parametric tests were employed because they are more powerful and make

better use of the available information in a dataset than their nonparametric counterparts (Weaver, 2002).

To offer further corroboration from the initial analyses, paired t-tests were conducted, which have been

shown to be reliable even with extremely small sample sizes (deWinter, 2013).

Effect sizes were calculated as described in Veehof et al. (2011). Cohen's *d* was computed to

estimate the effect size of 1) the mean change from baseline to endpoint and from baseline to follow-up

within the case group, and 2) the mean difference between case and control group at endpoint and at

follow-up. Hedges' *g*, a more conservative estimate of effect size, was also calculated to account for the

positive bias inherent in small sample sizes (Hedges, 1981). Effect sizes of 0.2, 0.5, and 0.8 are

recognized as small, medium, and large, respectively (Cohen, 1977). Eta squared (η^2) was computed to

determine the proportion of variance in dependent variables explained by independent factor effects for

the ANOVAs. Eta-squared values of .01, .06, and .14 are typically considered to be small, medium, and

large effects (Green & Salkind, 2003, p. 162).

For the PGIC, independent samples two-tailed *t*-tests were performed on continuous variables

(numeric ratings of change) and X^2 tests were carried out on ordinal data (reported symptom

improvement). The significance level for all statistical tests was p<.05. All statistical analyses were

completed using SPSS software (SPSS Inc., Chicago, Illinois); ANOVAs were run on SPSS version 21.

SPSS version 19 was used for all other statistical tests. Excel 2010 was used to calculate effect sizes

(η^2, *d*, *g*) and 95% confidence intervals, and to prepare graphs. Cohen's *d* and Hedges' *g* were computed

using a downloadable Excel calculator from the Centre for Evaluation & Monitoring (2013). (Centre for

Evaluation & Monitoring, 2013).

To determine the sample size required to detect an effect for future studies on mindfulness and

chronic pain, post-hoc power analyses were performed using G*Power software, Version 3.1.7 (Faul,

Universitat Kiel, Germany). These analyses focused on pain intensity and pain interference measures

that were found to be statistically significant among case group participants from baseline to follow-up.

<u>Study Hypotheses</u>

Primary Hypotheses:

1a) The case group will report at least a 20% decrease in pain intensity and pain interference from

baseline to endpoint on all primary outcome measures (VAS, BPI, DVPRS).

1b) The case group will report significantly larger decreases in pain intensity and pain interference from

baseline to endpoint as compared to the control group.

Secondary Hypotheses:

2a) The case group will report significant decreases in PTSD symptoms on the PCL-M.

2b) The case group will report significant decreases in depressive symptoms on the BDI-II.

2c) The case group will report significant increases in affective control on the ACS.

2d) The case group will report significant increases in mindfulness on the FFMQ.

2e) The case group will report significant increases in quality of life on the WHOQOL-BREF.

2f) The case group will demonstrate significant decreases in inattention on the CPT II.

2g) The case group will demonstrate significant decreases in impulsivity on the CPT II.

2h) The case group will demonstrate significant increases in vigilance on the CPT II.

2i) The case group will demonstrate significant decreases in IL-6 from baseline to endpoint.

2j) The case group will demonstrate normalization, or a trend towards normalization, of urinary cortisol

excretion from baseline to endpoint. The normal reference range for urinary free cortisol excretion will be

defined as within 4.0-50.0 mcg/24 hours.

CHAPTER 3

RESULTS

<u>Baseline Characteristics</u>

The attrition rate among participants who began the study (n=13) was 31% (n=4), all of whom

were case group members. Compared to those in the case group who were included in the final analysis,

excluded patients were on average younger (M=41.5 vs. 45.3), of lower BMI (M=30.0 vs. 32.4), lower

VAS pain intensity (M=5.5 vs. 6.8), and lower DVPRS interference (M=6.2 vs. 7.3). However, baseline

independent samples t-tests of case group members who were included (n=4) vs. those who were

excluded (n=4) confirmed that demographics (age, BMI, years of education) and all self-report measures

of pain (VAS, BPI, DVPRS) and emotional functioning (BDI, ACS, PCL-M, FFMQ) were nonsignificant

(p>>.05).

Intention to treat analyses were not performed for a number of reasons. Because the 3

noncompleters dropped out early in the study before midpoint measures were administered, prior data

was not available to impute measurement outcomes based upon the "last observation carried forward"

technique. Although baseline data was available to attempt "baseline observation carried forward," the

National Research Council argues that this technique is problematic due to the tendency for statistical

inferences to be distorted by bias and statistical precision to be inflated because imputed values are

presumed to be correct (NRC, 2010). These issues also apply to the participant who was removed from

the final analysis due to a fall resulting in loss of consciousness; this patient experienced his accident

before midpoint, which invalidated his midpoint, endpoint, and follow-up results. Replacing missing values

with the group mean at each time point was also considered, however this technique relies on the

assumption that the data was missing completely at random, which is not likely given the small sample.

Using the group mean for missing values would also underestimate the standard deviation and

consequently the standard error of the mean for each variable, leading to inflated statistical test values

and increased likelihood of committing a Type I error (Streiner, 2013). The Cochrane Collaboration

(2002) cautions that imputation of missing data for intention to treat analyses is controversial, and

particularly difficult with continuous measures, as was the case with the primary outcome measures in the

present study. Therefore, the investigators decided not to attempt to employ imputation techniques to account for missing data in the current study.

Study participants were African American (n=5), Hispanic (n=2), Polynesian (n=1) and White (n=1; Figure 2). Highest level of education completed and total annual household income were broadly distributed. A larger number of case group patients completed undergraduate education or earned a total annual household income of $66K-80K (Figure 3), whereas more control group members received masters degrees or earned $36-50K (Figure 4). Half of the participants in the case group exercised regularly compared with 60% in the control group (Figure 5).
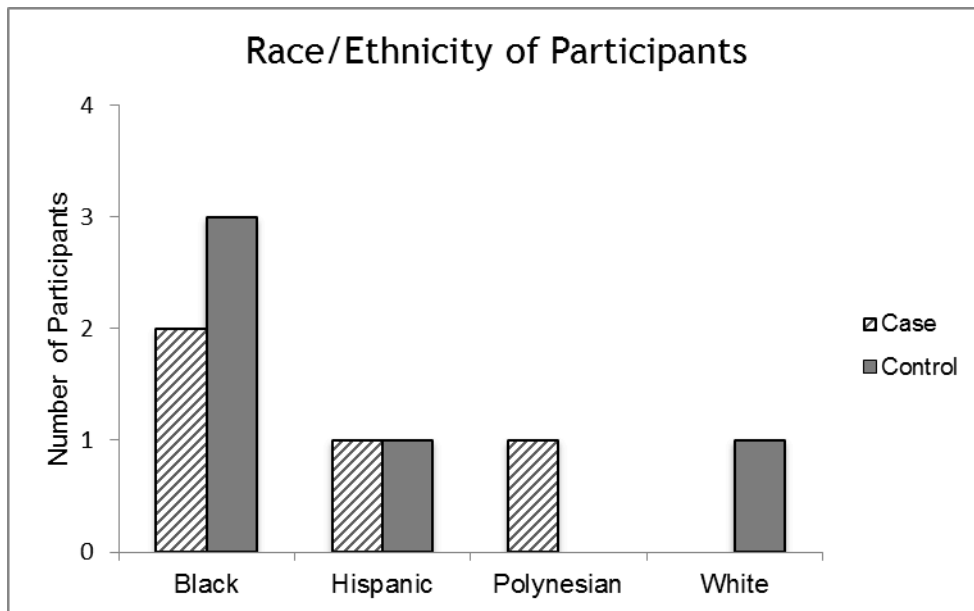
Figure 2. Reported Race/Ethnicity of Participants in Case (n=4) and Control (n=5) Groups.
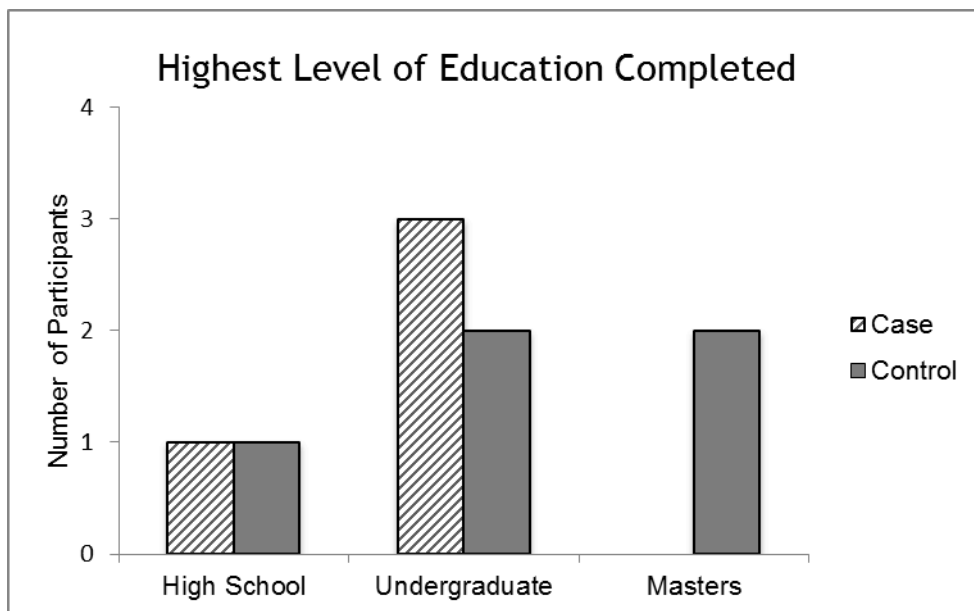
Figure 3. Highest Reported Level of Education Completed.
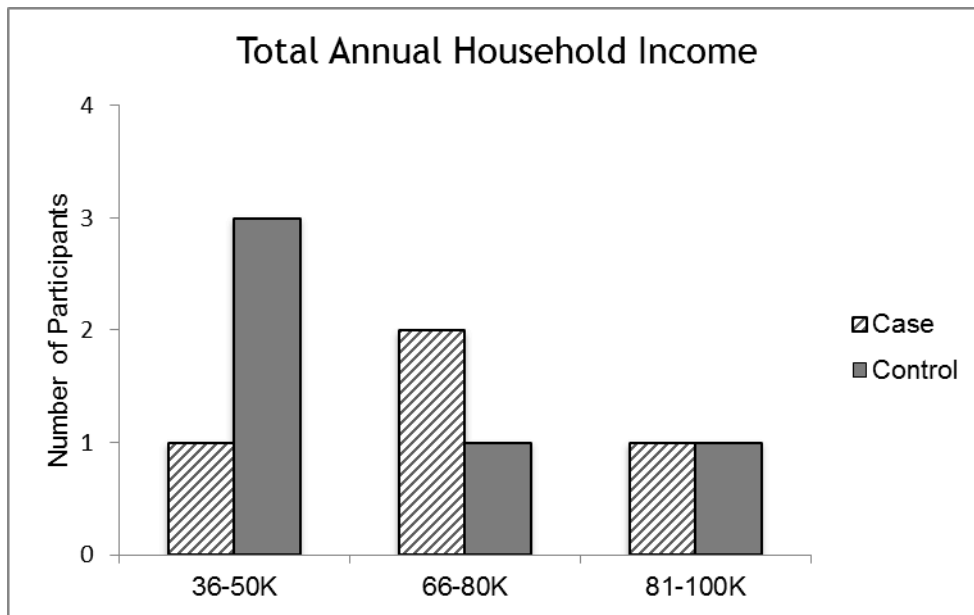
Figure 4. Reported Total Annual Household Income.
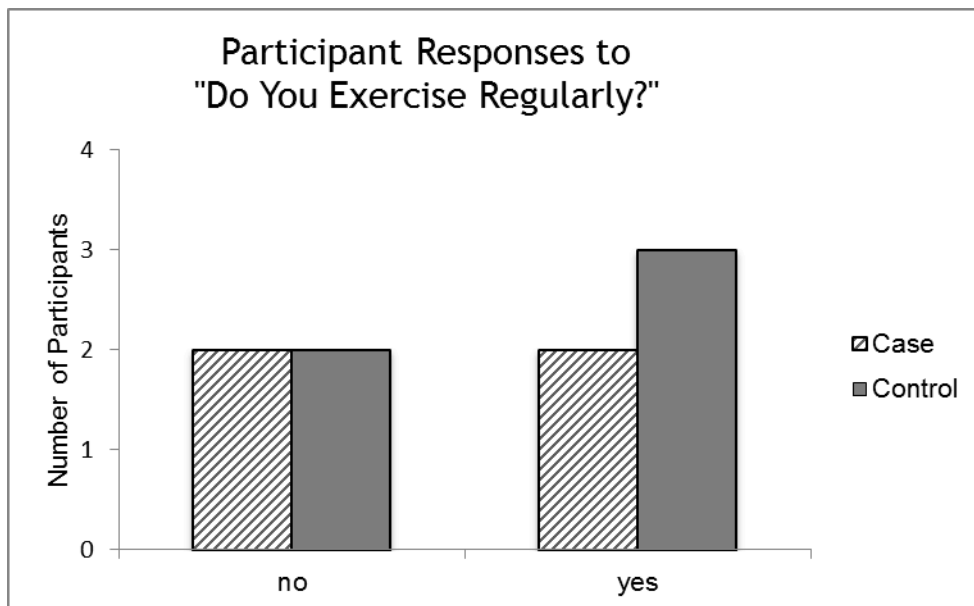
Figure 5. Case and Control Group Responses to the Question, "Do you exercise regularly?"

Participants primarily served in the Army (n=7) and were deployed to combat zones prior to OEF/OIF (n=6; Table 3). Clinical pain evaluation data at baseline shows that pain symptoms reported by patients in both groups (n=9) were primarily musculoskeletal, located in the low back (n=7), knees (n=5), neck (n=3), hips (n=2), and shoulders (n=2; Figure 6, Table 3). Most participants experienced pain in more than one region, with the majority reporting two distinct regions (n=4), followed by three (n=2) and four (n=2) different areas of pain (Figure 7; Table 3). Two patients had a partially contributing neuropathic pain component, in the form of lumbar radiculopathy.

At baseline, case and control group patients did not statistically differ on demographic characteristics (age, BMI, years of education), self-reported pain intensity (VAS, DVPRS-NRS, BPI-Sev), or measures of emotional functioning and quality of life (BDI, FFMQ, ACS, PCL-M, WHOQOL; $p>.05$; Table 4). BDI scores and both measures of pain interference (DVPRS and BPI) were higher on average for the case group at baseline, although this did not reach statistical significance $(p>.05$; Table 4).

Table 3

Participant Demographics and Self-reported Pain at Baseline for the Clinical Pain Evaluation

	Deployments	Pain Area	now	max	min	avg
Case Participants	OEF/OIF Bosnia	knee	9	10	6	5
		neck	9	10	4.5	5
		low back	4	9	3	3
		hip	3	5	2	2
	OIF Desert Storm	feet	5	9	2	5
		low back	2	8	2	2
		shoulder	2	8	2	2
	OIF Desert Storm	low back rad	8	8	5	7
		knee	5	7	4	6
	OEF/OIF Kosovo	low back rad	7	8	6	7
		neck	6	9	6	6.5
Control Participants	OIF Bosnia	low back	5	6	4	5
		shoulder	4	5	4	5
	OIF Desert Storm	chest	6	8	3	6
		hip	6	7	5	6
		low back	5	8	4	6
		knee	4	7	4	6
	OIF	ear	5	8	4	6
	OEF	knee	7	10	5	7
		low back	6	8	6	6
	OIF	neck	9	10	5	8
		knee	6	9	5	8
		wrist	5	7	5	5

Note. OEF=Operation Enduring Freedom (Afghanistan), OIF=Operation Iraqi Freedom. rad=radiculopathy. now=pain level now. max=maximum, min=minimum and avg=average pain in the past 24 hours.
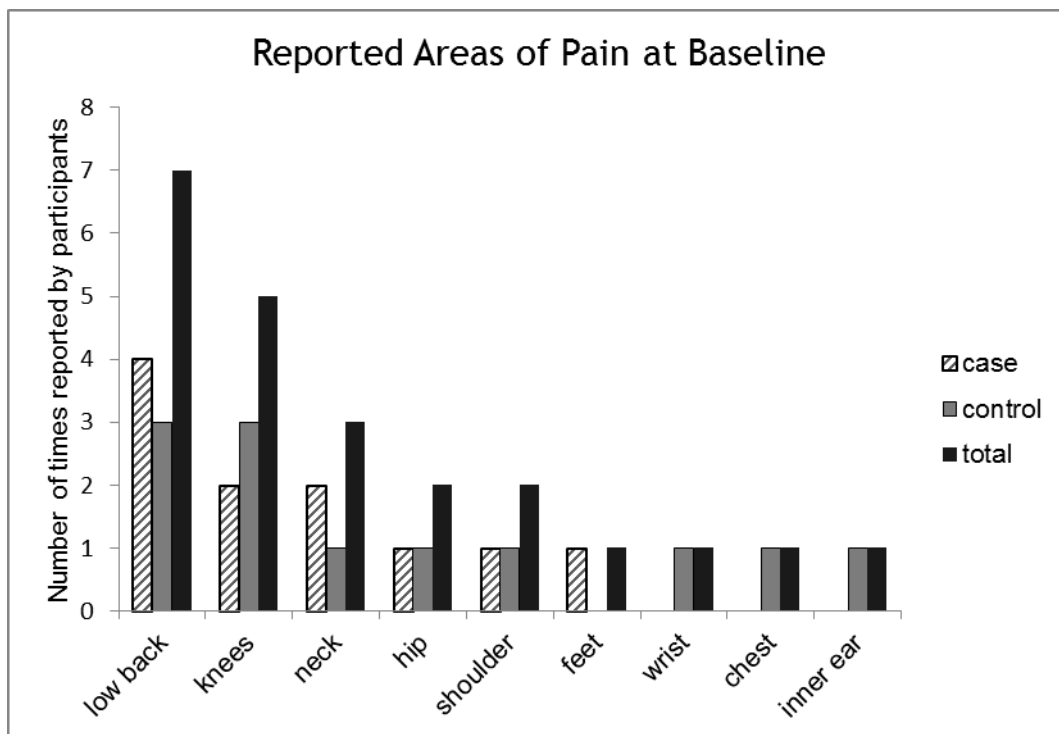
Figure 6. Pain Areas Reported During the Clinical Pain Evaluation.
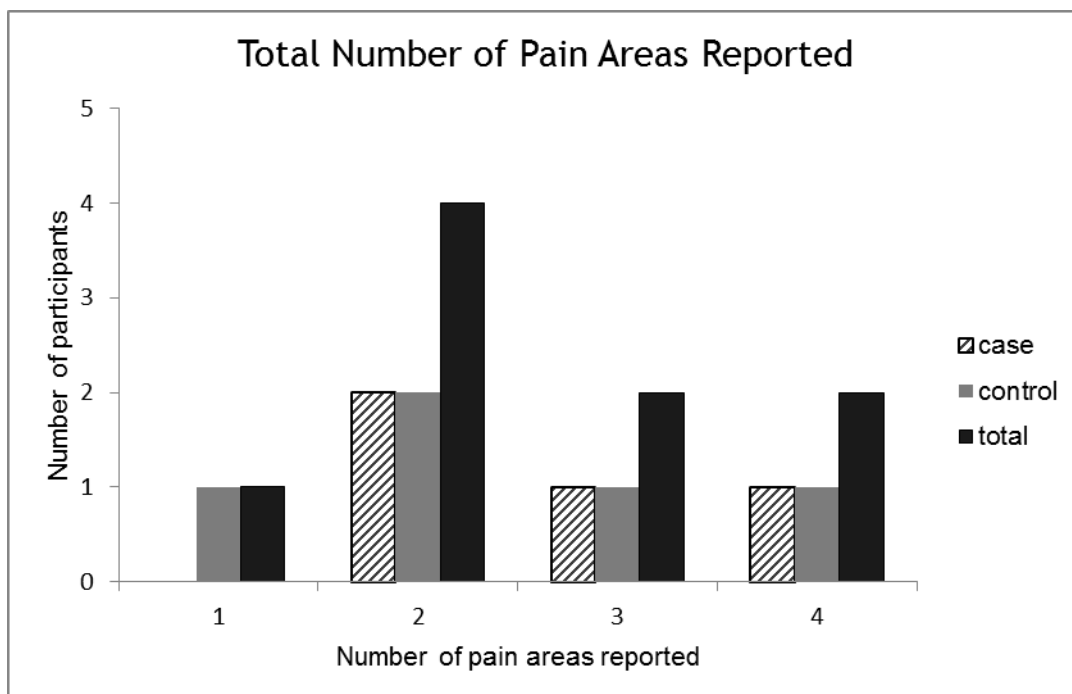
Figure 7. Total Number of Pain Areas Reported During the Clinical Pain Evaluation.

Table 4

Independent Samples t-tests of Baseline Characteristics and Measures

		n	M	SD	t	df	p
Age	CASE	4	45.25	1.50	-1.04	7	.33
	CONTROL	5	49.60	8.11			
BMI	CASE	4	32.38	3.86	1.54	7	.17
	CONTROL	5	28.37	3.92			
Years of Education	CASE	4	14.63	0.75	0.18	7	.86
	CONTROL	5	14.40	2.30			
VAS	CASE	4	67.8	18.6	0.42	7	.68
	CONTROL	5	64.0	6.7			
DVPRS (NRS)	CASE	4	6.50	2.08	0.19	7	.85
	CONTROL	5	6.30	0.97			
BPI (Sev)	CASE	4	6.63	1.11	0.75	7	.49
	CONTROL	5	6.15	0.80			
DVPRS (Int)	CASE	4	7.31	2.49	1.28	7	.24
	CONTROL	5	5.45	1.89			
BPI (Int)	CASE	4	7.54	1.73	1.19	7	.27
	CONTROL	5	5.84	2.36			
BDI	CASE	4	25.50	10.47	1.16	7	.29
	CONTROL	5	16.60	12.14			
FFMQ	CASE	4	120.50	18.45	-0.77	7	.46
	CONTROL	5	131.20	22.10			
ACS	CASE	4	151.50	24.34	0.16	7	.87
	CONTROL	5	146.60	54.84			
PCL-M	CASE	4	43.00	11.61	-.069	7	.51
	CONTROL	5	51.90	23.50			
WHOQOL	CASE	4	80.00	17.34	-0.46	6	.66
	CONTROL	4	86.75	23.53			

Note. BMI = body mass index, VAS = visual analog scale, DVPRS = Defense and Veterans Pain Rating Scale, BPI = Brief Pain Inventory, NRS=numeric rating scale, Sev=severity subscale, Int=interference subscale, n=number of participants, M=mean, SD = standard deviation, *t*=*T*-statistic, df = degrees of freedom. p-value is significant at p<0.05, two-tailed. Because one control group participant did not complete every item of the WHOQOL-BREF, only n=8 participants were included in this analysis.

Pain Intensity and Interference

Mean pain intensity on the VAS and DVPRS (NRS) decreased from baseline to endpoint (B-E) (Figures 8-9). However, the percentage reduction on these measures was greater for the case vs. control group (Table 5). For the case group, pain reduction on the NRS (26.92%) was sustained at follow-up (26.92%), but only partially maintained for the VAS (42.44% at endpoint vs. 22.51% at follow-up). All decreases in pain intensity for the case group were of minimal (20-30%) or moderate (>30%) clinical importance. The control group did not achieve a minimally significant change for all pain measures and time intervals (<20%).

Similar trends were observed for pain intensity on the BPI (Figure 10). Although BPI severity scores declined from B-E in both groups, average pain reduction for the case group (23.58%) was greater than the control group (4.88%; Table 5). Improvements in pain severity were somewhat reverted at follow-up for the case group (9.43%), compared with slightly worsened pain intensity in the control group (-13.82%). Overall, the case group presented greater variance in pain scores compared to the control group at all time points and measures of pain intensity as revealed by 95% confidence intervals (Figures 8-10).

At baseline, mean pain interference on the DVPRS and BPI were clinically higher for the case group (*M*=7.31, *SD*=2.49; *M*=7.54, *SD*=1.73) than the control group (*M*=5.45, *SD*=2.88; *M*=5.84; *SD*=2.36; Figures 11-12). For the case group, pain interference substantially decreased from B-E on the DVPRS (41.06%) and BPI (32.72%), and these improvements were generally maintained at follow-up (34.22% and 33.65% respectively; Table 5). For the control group, changes in pain interference across measures and time points were not clinically significant (<10%; Table 5).

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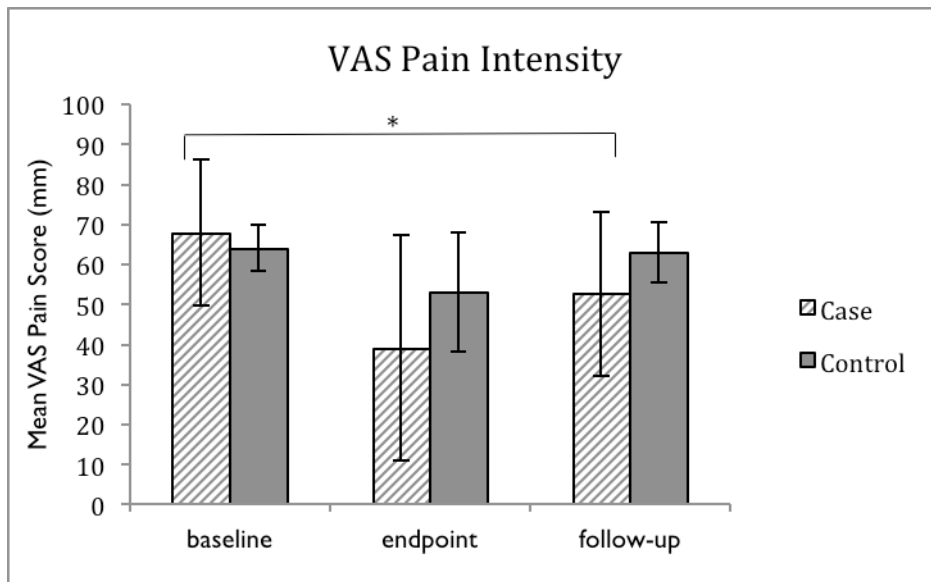
Figure 8. Mean Visual Analog Scale (VAS) Pain Scores and 95% Confidence Intervals Over Time.
* = significant result (p<.05)
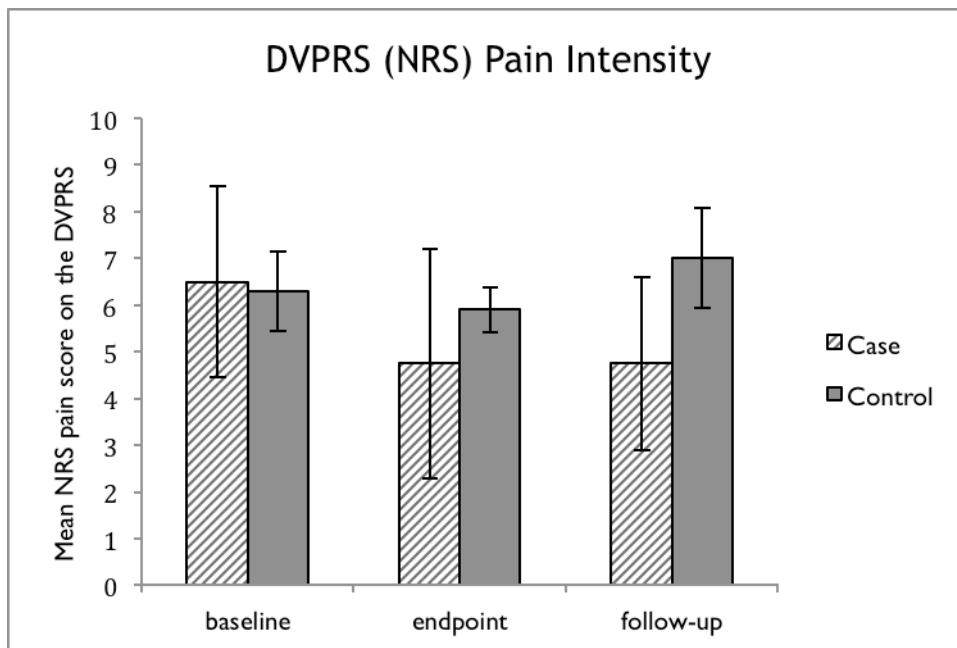
Figure 9. Mean Numeric Pain Rating Scale (NRS) on the Defense and Veterans Pain Rating Scale (DVPRS) and 95% Confidence Intervals Over Time.

Table 5

Percentage Reduction in Mean Pain Scores from Baseline to Endpoint and from Baseline to Follow-up

Pain measure	Time point	Case	Control
VAS	B-E	42.44%	17.19%
	B-F	22.51%	1.88%
DVPRS (NRS)	B-E	26.92%	6.35%
	B-F	26.92%	-11.11%
BPI (Sev)	B-E	23.58%	4.88%
	B-F	9.43%	-13.82%
DVPRS (Int)	B-E	41.06%	8.26%
	B-F	34.22%	-3.67%
BPI (Int)	B-E	32.72%	7.07%
	B-F	33.65%	4.16%

Note. B=baseline, E=endpoint; F=follow-up. Positive percentages represent mean reductions in pain and negative percentages are mean increases in pain. Minimally and moderately important changes in pain are defined as 20-30% and >30%, respectively (Dworkin et al., 2008)
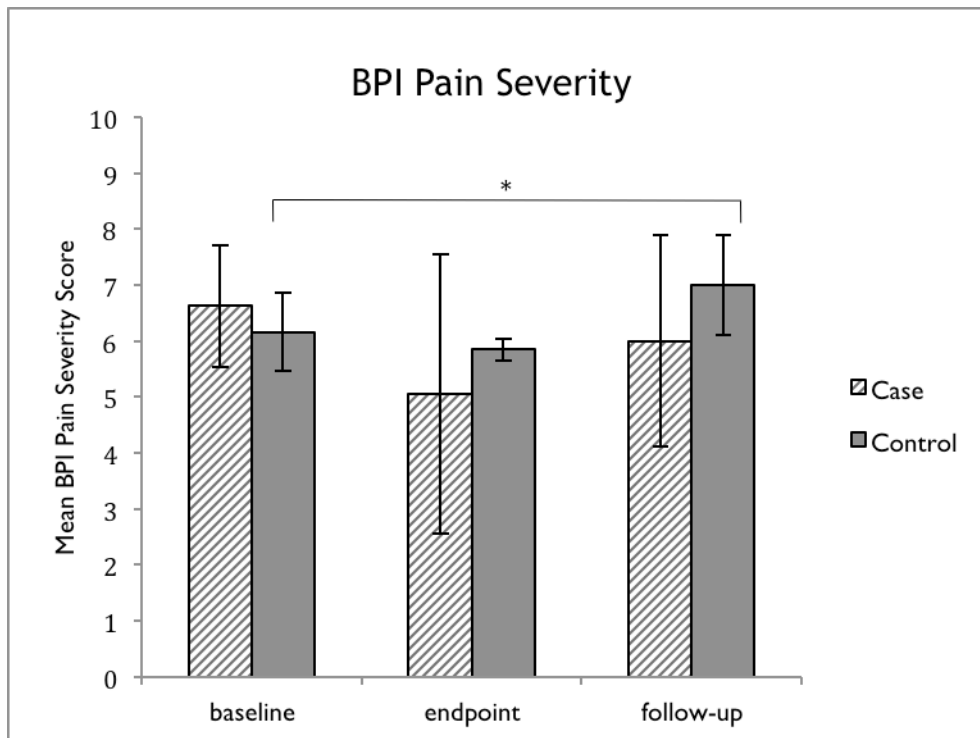
Figure 10. Mean pain severity scores on the Brief Pain Inventory (BPI) and 95% Confidence Intervals Over Time. * = significant result (p<.05)
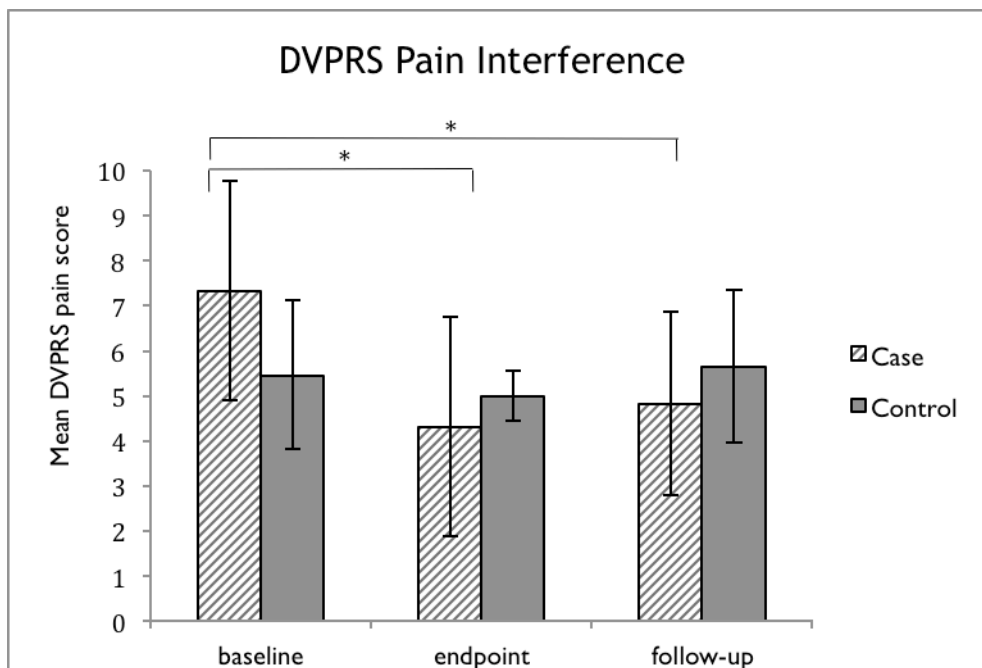
Figure 11. Defense and Veterans Pain Rating Scale (DVPRS) supplemental item scores and 95% Confidence Intervals Over Time. * = significant result (p<.05)
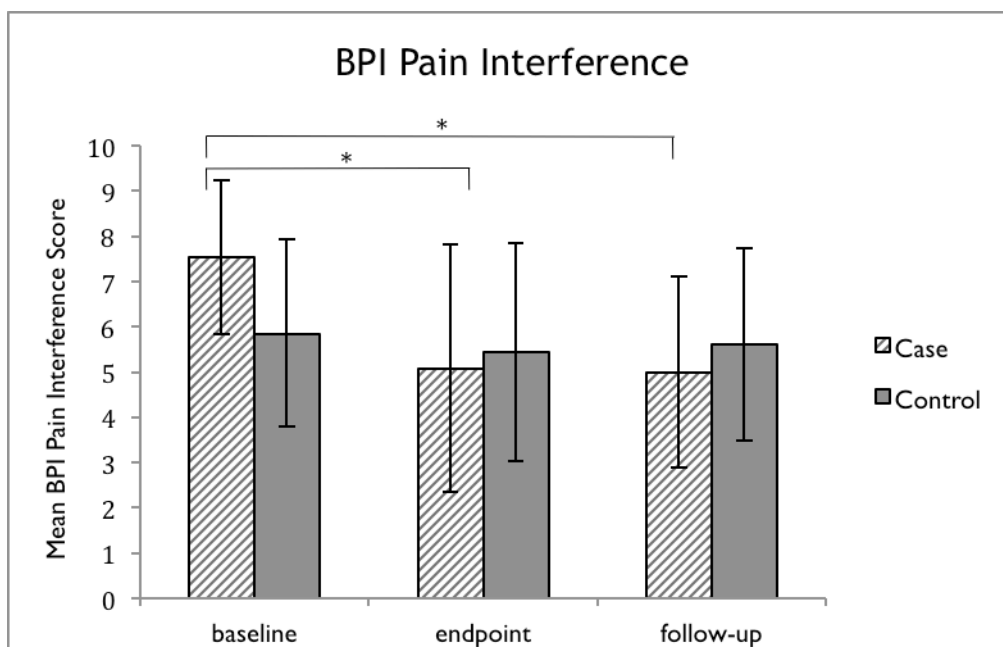
Figure 12. Mean Pain Interference Scores on the Brief Pain Inventory (BPI) and 95% Confidence Intervals Over Time. * = significant result (p<.05)

For the case group, all pain measures showed a decreasing trend from B-E (Figures 13 and 15). Most measures somewhat reverted at follow-up except for the NRS and BPI interference, which leveled out. Pain intensity and interference measures were more uniform across time points for the control group (Figures 14 and 16) except for trending increases in pain intensity from endpoint to follow-up (Figure 15). Among both groups, mean VAS and NRS pain intensity scores were more closely correlated at baseline and endpoint than BPI severity ratings (Figures 13 and 14).

Figures 17-20 depict pain intensity and pain interference scores on the DVPRS, as reported by individual participants. For pain intensity, 3 of 4 case group participants (75%) showed decreasing trends in pain intensity from B-E compared with 2 of 5 control participants (40%; Tables 17-18). The same proportion of participants in the case and control group presented lowered apparent intensity scores from B-F (Tables 17-18). Pain interference for all case group participants followed a decreasing trend from B-E and displayed a lower apparent score from B-F (Figure 19). In comparison, 2 of 5 control participants (40%) showed decreasing trends in pain interference and only 1 participant (20%) had a lower apparent score from B-F (Figure 20).
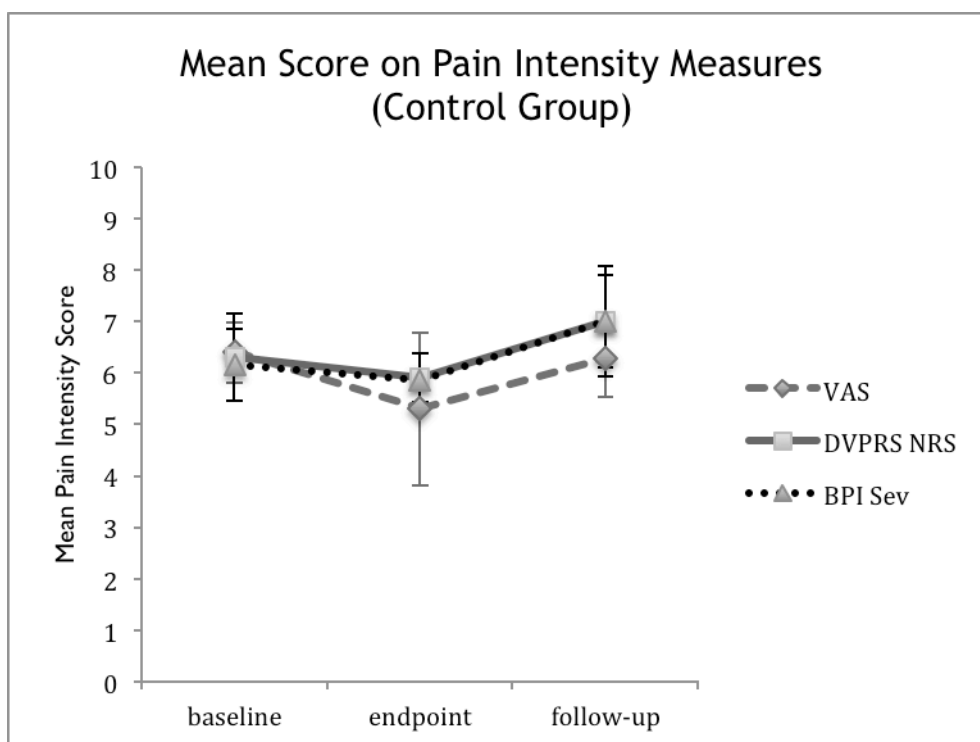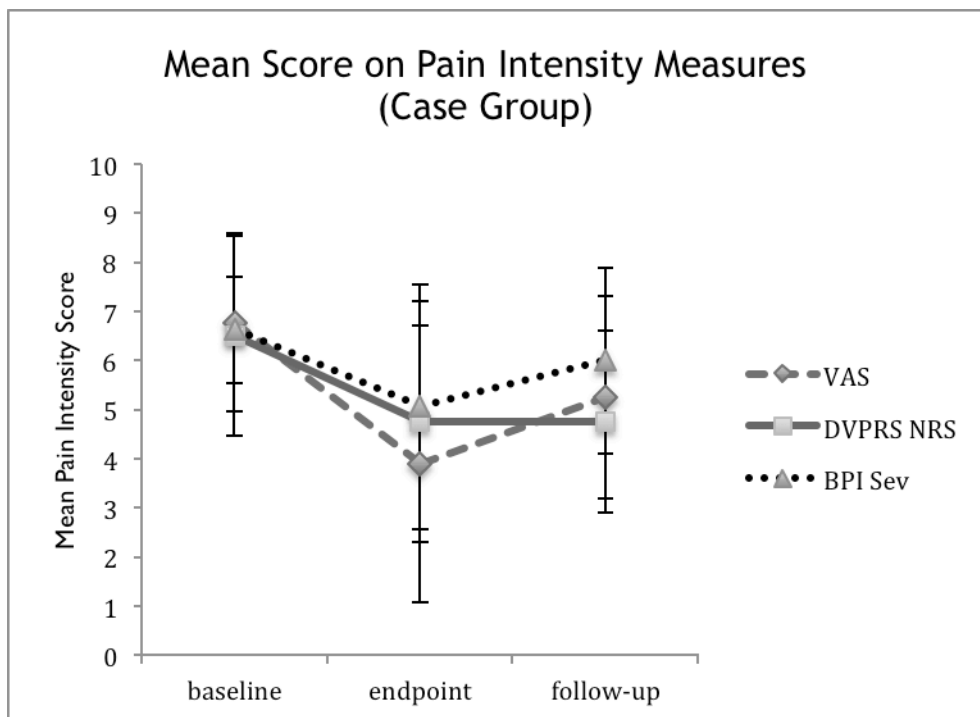
Figures 13 and 14. Mean Score on Three Different Measures of Pain Intensity. VAS values were divided by a factor of 10 for purposes of comparison with other pain measures on a 10-point scale.
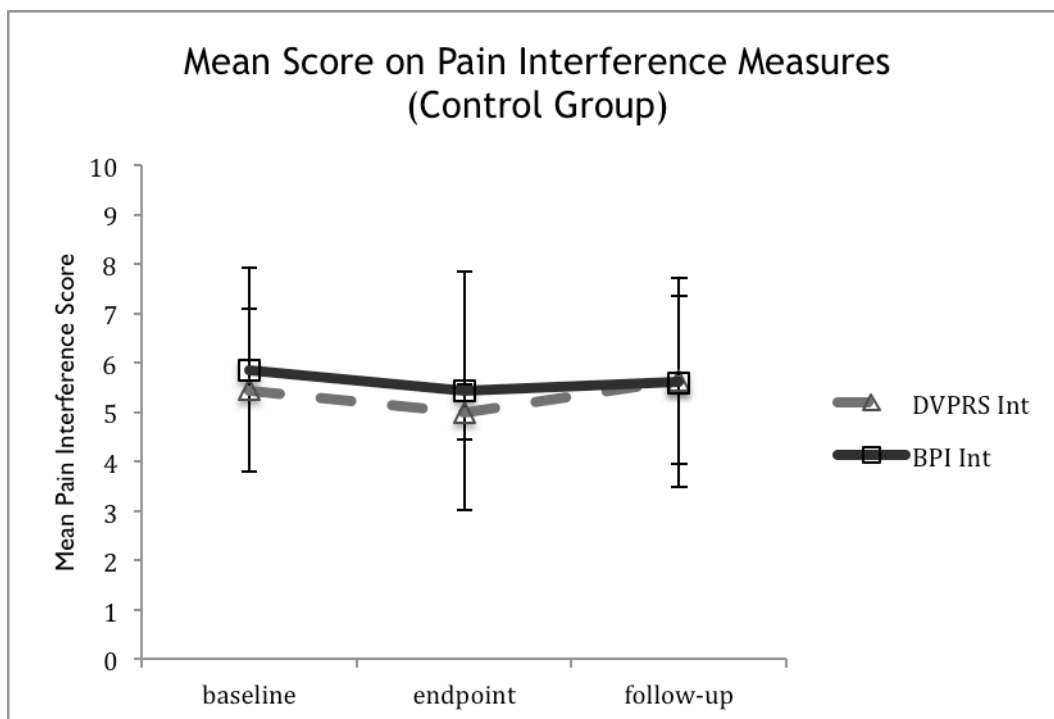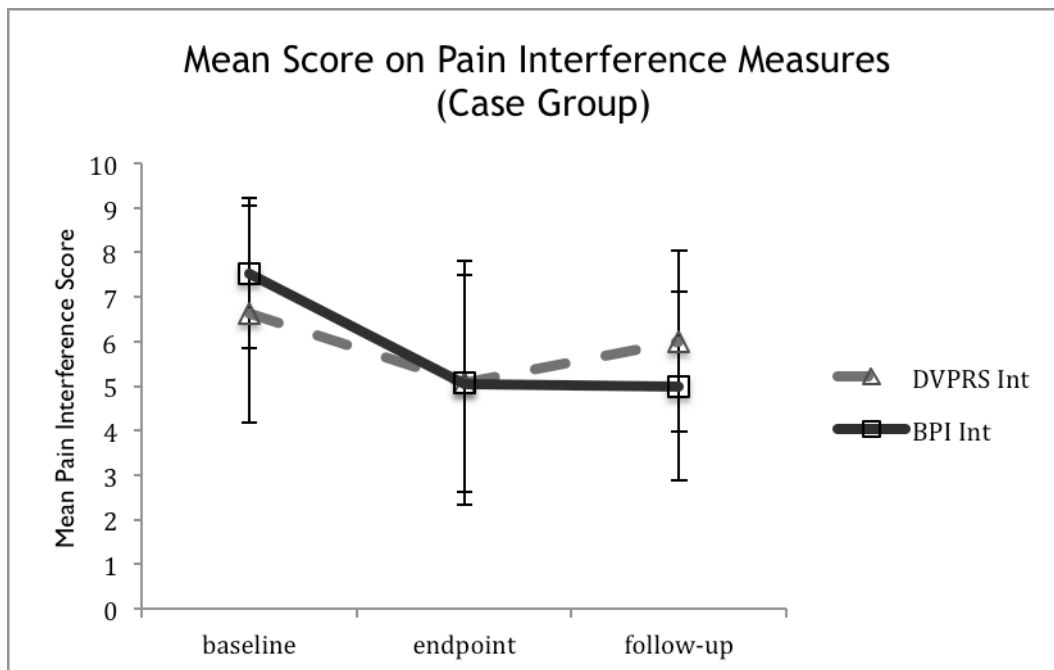
Figures 15 and 16. Mean Score on Two Different Measures of Pain Interference.
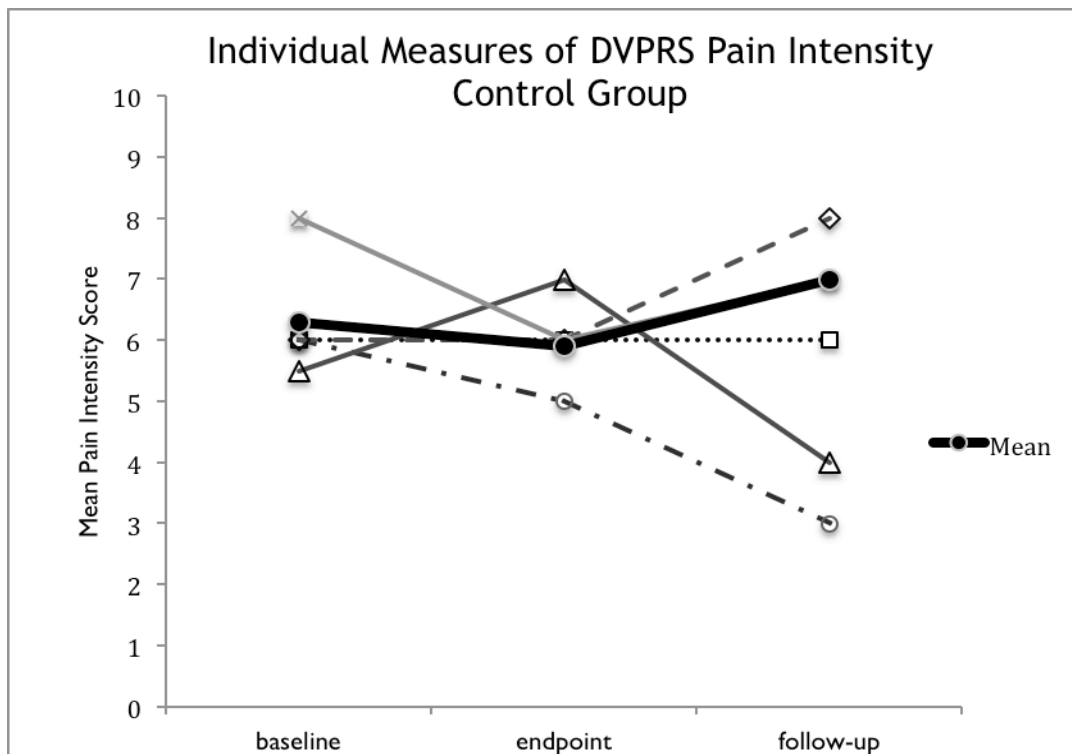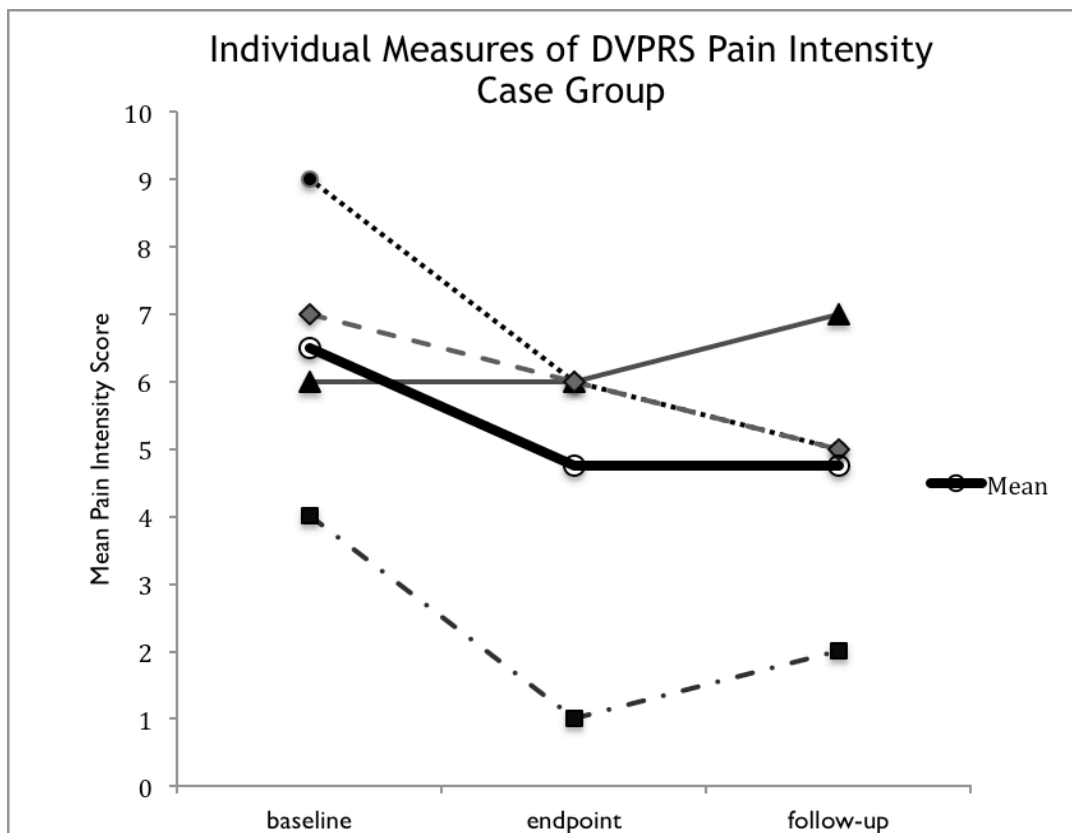
Figures 17 and 18. Individual Measures of Pain Intensity on the DVPRS for Case and Control Groups.
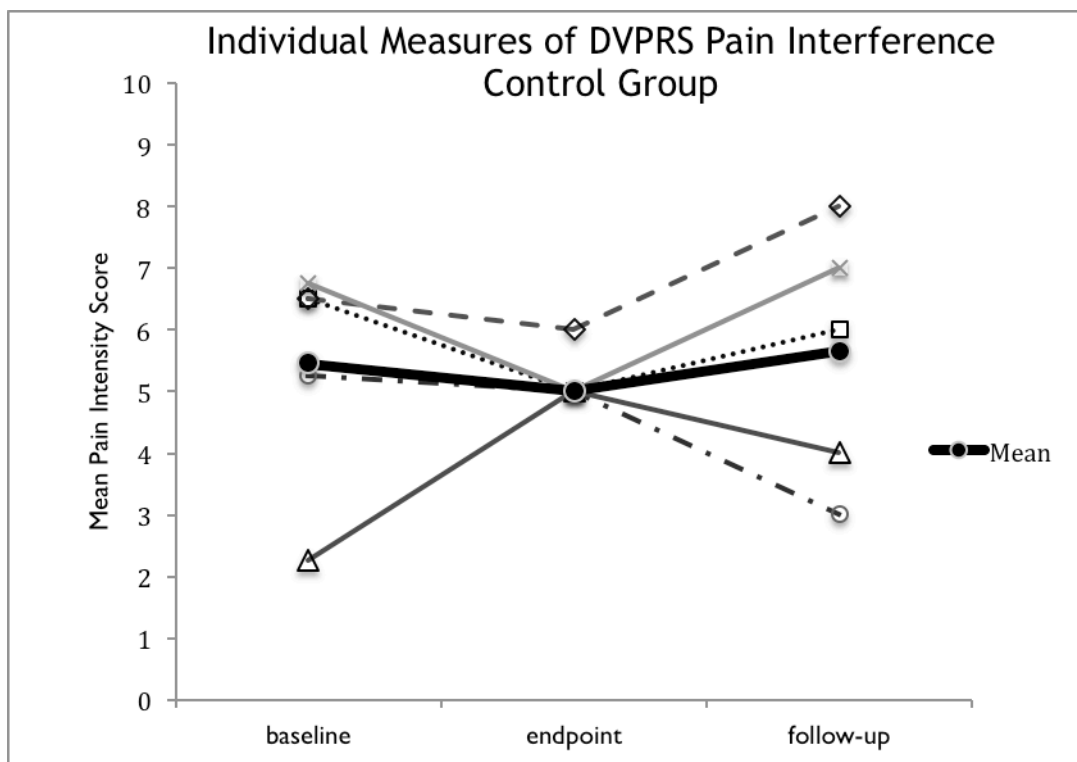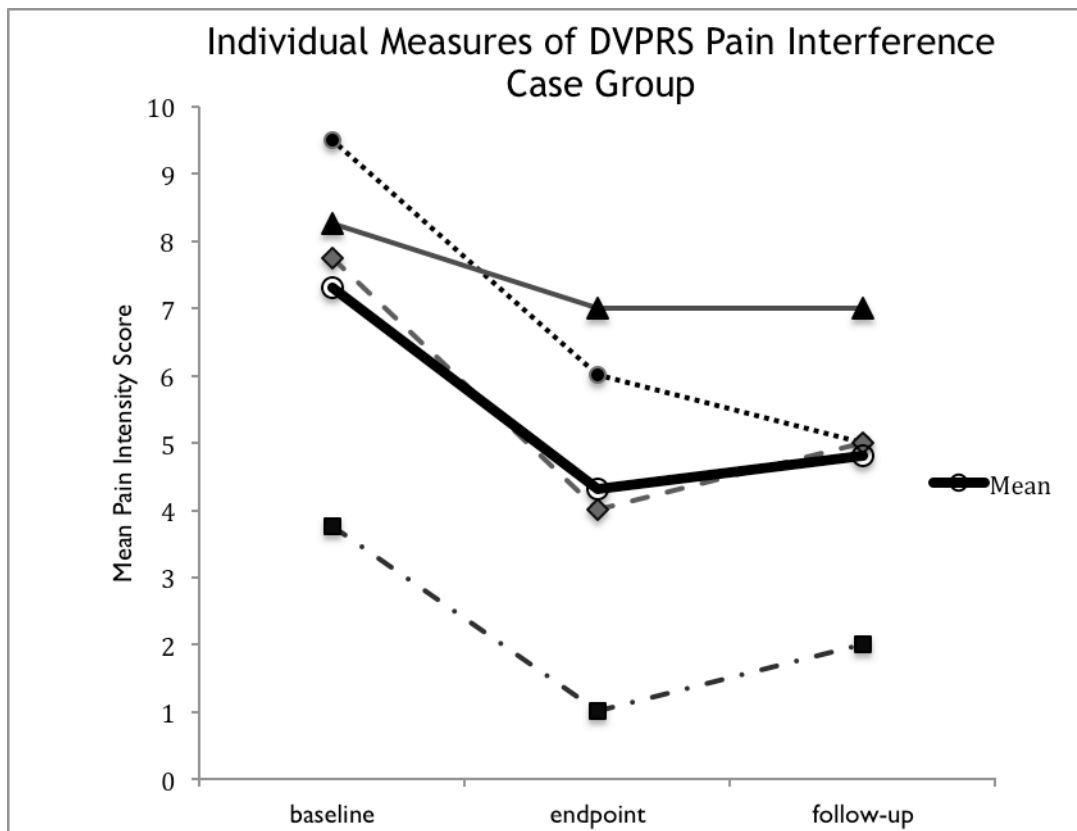
Figures 19 and 20. Individual Measures of Pain Interference on the DVPRS for Case and Control Groups.

Two-factor mixed ANOVA findings are provided in Table 6. The main effect of time was significant from B-E for two measures of pain intensity (VAS: $p=.032$; NRS: $p=.044$) and from baseline to follow-up (B-F) for the VAS $(p=.029)$. A time by group interaction effect was found from B-F for both the NRS $(p=.021)$ and BPI severity $(p=.019)$; a trending result was found for the VAS $(p=.053)$ between these time points. Pain interference measures (BPI and DVPRS) were significant at all time intervals for both the main effect and interaction between time and group, except for B-E for the BPI which demonstrated a trending result for the interaction effect $(p=.074)$.

Paired *t*-tests revealed that the VAS pain intensity decreased from B-F for the case group $(p=.041$; Table 7, Figure 8). In addition, lowered pain interference scores were found from B-E and from B-F on the DVPRS $(p=.013; p=.032$; Figure 11) and BPI $(p=.047; p=.012$; Table 7; Figure 12). For the control group, the only significant finding was an increase in BPI pain severity from B-F $(p=.003$; Table 7, Figure 10).

Large effect sizes were observed between time points for all pain interference measures in the case group $(g=0.92–1.13$; Table 7). Pain intensity measures were predominantly of medium effect size $(g=0.35–1.03)$. In comparison, effect sizes between groups were small to medium for pain intensity $(g=0.37–0.61)$ and small or no effect for pain interference $(g=0.12–0.37$; Table 7).

Table 6

ANOVA Results for Changes in Pain Intensity and Interference over Time between Case and Control Groups

			df	F	η^2	p
VAS	B-E	Time	1,7	7.14	.248	.032*
		Time * Group		1.42	.050	.272
	B-F	Time	1,7	7.44	.088	.029*
		Time * Group		5.43	.064	.053▽
DVPRS (NRS)	B-E	Time	1,7	6.02	.114	.044*
		Time * Group		2.37	.045	.167
	B-F	Time	1,7	1.63	.027	.243
		Time * Group		8.85	.145	.021*
BPI (Sev)	B-E	Time	1,7	5.15	.122	.057▽
		Time * Group		2.37	.056	.168
	B-F	Time	1,7	.22	.002	.656
		Time * Group		9.30	.099	.019*
DVPRS (Int)	B-E	Time	1,7	13.18	.177	.008**
		Time * Group		7.23	.097	.031*
	B-F	Time	1,7	5.96	.077	.045*
		Time * Group		8.22	.107	.024*
BPI (Int)	B-E	Time	1,7	8.69	.091	.021*
		Time * Group		4.41	.046	.074▽
	B-F	Time	1,7	39.09	.102	.000**
		Time * Group		26.62	.069	.001**

Note. E=endpoint; B=baseline, F=follow-up, Time = main effect, Time * Group = interaction effect. η^2=effect size (eta squared). **p<0.01; *p<0.05. ▽trending result (0.05<p<0.1)

Table 7

Paired t-test Results for Pain Intensity and Interference Measures between Baseline-Endpoint and Baseline-Follow-up

			n	M	SD	t	df	p	d	g
VAS	B-E	CASE	4	28.75	25.68	2.24	3	.111	1.19	1.03
		CONTROL	5	11.00	19.14	1.29	4	.268	0.62	0.55
	B-F	CASE	4	15.25	8.85	3.45	3	.041*	0.77	0.67
		CONTROL	5	1.20	9.09	0.295	4	.783	0.68	0.60
DVPRS (NRS)	B-E	CASE	4	1.75	1.50	2.33	3	.102	0.76	0.66
		CONTROL	5	0.40	1.14	0.78	4	.477	0.68	0.61
	B-F	CASE	4	1.75	1.71	2.05	3	.133	0.88	0.76
		CONTROL	5	-0.70	0.67	-2.33	4	.080▽	0.42	0.37
BPI (Sev)	B-E	CASE	4	1.56	1.49	2.10	3	.127	0.80	0.69
		CONTROL	5	0.30	0.97	0.69	4	.529	0.47	0.42
	B-F	CASE	4	.63	1.05	1.19	3	.320	0.40	0.35
		CONTROL	5	-0.85	0.29	-6.67	4	.003**	0.67	0.60
DVPRS (Int)	B-E	CASE	4	3.00	1.14	5.28	3	.013*	1.21	1.05
		CONTROL	5	0.45	1.59	.631	4	.562	0.41	0.36
	B-F	CASE	4	2.50	1.32	3.78	3	.032*	1.09	0.95
		CONTROL	5	-0.20	1.46	-.306	4	.775	0.42	0.37
BPI (Int)	B-E	CASE	4	2.46	1.50	3.28	3	.047*	1.06	0.92
		CONTROL	5	0.41	1.42	0.65	4	.549	0.13	0.12
	B-F	CASE	4	2.54	0.94	5.42	3	.012*	1.30	1.13
		CONTROL	5	0.24	0.33	1.63	4	.179	0.26	0.23

Note. E=endpoint; B=baseline, F=follow-up. *M*=mean difference, *SD*=standard deviation of the mean difference, *df*=degrees of freedom, *t*=*T*-value (two-tailed at significance level p<0.05), *d*=Cohen's d, *g*=Hedges' G. Effect sizes (*d* and *g*) listed in the CONTROL rows were calculated based upon the difference between case and control groups at endpoint or follow-up. **p<0.01, *p<0.05, ▽trending result (0.05<p<0.1).

ANOVA tests for emotional functioning measures showed a significant main effect of time for the BDI-II from B-F *(p=.028)* and a trending result from B-E *(p=.098)*. There was also a significant time by group interaction from B-E *(p=.037; Table 8)*. Further analysis was carried out on individual mood items on the DVPRS and BPI ("how pain has interfered with your mood during the past 24 hours"). Significant main effects of time and interaction effects for time by group were found for both measures of mood except for the time main effect for BPI from B-E (*p*=.112) and a trending interaction effect for the DVPRS from B-F (*p*=.055; Table 9). Sleep items on the DVPRS and BPI ("how pain has interfered with your sleep during the past 24 hours") were also analyzed. Significance was only demonstrated for the DVPRS; a time main effect *(p=.019)* and trending interaction effect *(p=.068)* from B-E, and a significant interaction effect from B-F *(p=.007; Table 9)*.

For the FFMQ, trending results were detected from B-F for the main effect of time *(p=.074)*, and time by group interactions were observed for both B-E *(p=.097)* and B-F *(p=.065; Table 8)*. Subscales of the FFMQ were subsequently analyzed to discover a main effect of time, $F(1,7)=23.92$, $p=.002$, $\eta^2=.035$ and an interaction between time and group, $F(1,7)=15.43$, $p=.006$, $\eta^2=.023$ for the Act with Awareness items of this mindfulness questionnaire. All other measures of emotional functioning and quality of life (ACS, PCL-M, WHOQOL-BREF) did not achieve statistical significance *(p>.10; Table 8)*.

Table 8

ANOVA Results for the Change in Emotional Functioning and Quality of Life over Time between Case and Control Groups

			df	F	η²	p
BDI-II	B-E	Time	1,7	3.65	.019	.098∇
		Time * Group		66.74	.035	.037*
	B-F	Time	1,7	7.67	.091	.028*
		Time * Group		1.56	.018	.252
FFMQ	B-E	Time	1,7	0.27	.002	.622
		Time * Group		3.66	.029	.097∇
	B-F	Time	1,7	4.42	.018	.074∇
		Time * Group		4.76	.019	.065∇
ACS	B-E	Time	1,7	0.88	.008	.380
		Time * Group		0.02	.000	.900
	B-F	Time	1,7	0.71	.004	.429
		Time * Group		0.81	.005	.399
PCL-M	B-E	Time	1,7	1.63	.010	.242
		Time * Group		1.19	.007	.312
	B-F	Time	1,7	0.30	.001	.599
		Time * Group		0.75	.002	.415
WHOQOL	B-E	Time	1,6	2.79	.010	.146
		Time * Group		0.08	.000	.794

Note. E=endpoint; B=baseline, F=follow-up, Time = main effect, Time * Group = interaction effect. η²=effect size (eta squared). **p<0.01; *p<0.05. ∇trending result (0.05<p<0.1). Because one control group participant did not complete every item of the WHOQOL-BREF, only n=8 participants were included in the analysis.

Table 9

ANOVA Results for the Change in Mood and Sleep Item Scores on the DVPRS and BPI

			df	F	η^2	p
DVPRS (mood)	B-E	Time	1,7	26.07	.147	.001**
		Time * Group		15.89	.090	.005**
	B-F	Time	1,7	8.65	.110	.022*
		Time * Group		5.28	.067	.055▽
BPI (mood)	B-E	Time	1,7	3.31	.055	.112
		Time * Group		5.95	.099	.045*
	B-F	Time	1,7	25.94	.076	.001**
		Time * Group		14.44	.043	.007**
DVPRS (sleep)	B-E	Time	1,7	9.27	.220	.019*
		Time * Group		4.64	.110	.068▽
	B-F	Time	1,7	3.46	.029	.105
		Time * Group		14.44	.122	.007**
BPI (sleep)	B-E	Time	1,7	1.96	.074	.204
		Time * Group		1.42	.053	.272
	B-F	Time	1,7	0.92	.027	.369
		Time * Group		0.482	.014	.510

Note. E=endpoint; B=baseline, F=follow-up, Time = main effect, Time * Group = interaction effect. η^2=effect size (eta squared). **p<0.01; *p<0.05. ▽trending result (0.05<p<0.1)

Paired *t*-tests demonstrated a trending result for the BDI-II *(p=*.051) towards decreased depressive symptoms from baseline (*M=*25.5, *SD=*10.47) to endpoint (*M=*18.75, *SD=*9.50) in the case group (Table 10). This decrease in the BDI ($\geq$ 5 points) is recognized as clinically important (Dworkin et al. 2008). In addition, mood subscales for the DVPRS and BPI were significant (p<.05) for both time intervals (Table 11). A trending negative correlation was also found between frequency of iRest audio practice among case group participants and the difference in BDI scores from B-F, *r=-*.921, *N=*4, *p=*.079.

Although the cumulative FFMQ score was not significant from B-F in the case group *(p=*.103; Table 10), the Act with Awareness subscale was significant between these time points, *t*(3) = -4.62, *p=*.019 towards increased mindfulness. PCL-M scores trended towards increased PTSD symptoms *(p=*.077) from B-E in the case group. Sleep subscales were significant for the DVPRS at both time intervals (*p=*.035), trending for the BPI from B-E (*p=*.080), and not significant from B-F (*p=*.141; Table 11). No change was observed in the control group for any emotional functioning measure (Table 10) or subscale (Table 11).

Medium to large effect sizes between time points were found for BDI-II measures of depression (*g=*0.59, 0.83; Table 10), mood subscales for the DVPRS and BPI (*g=*1.01–1.31; Table 11), and most sleep subscales (*g=*0.46–1.19; Table 11) in the case group. Mindfulness showed small effect sizes (*g=*0.43, 0.47; Table 10). In comparison, between group effect sizes were small to no effect for all emotional functioning measures (*g=*0.00–0.28), except for sleep subscales which were larger in size (*g=*0.10–0.71; Tables 10-11).

Table 10

Paired t-test Results for Emotional Functioning and Quality of Life

			n	M	SD	t	df	p	d	g
BDI-II	B-E	CASE	4	6.75	4.27	3.16	3	.051∇	0.68	0.59
		CONTROL	5	-1.00	4.64	-.048	4	.655	0.11	-0.10
	B-F	CASE	4	9.50	9.04	2.10	3	.126	0.95	0.83
		CONTROL	5	3.60	5.08	1.59	4	.188	0.28	-0.25
FFMQ	B-E	CASE	4	-8.00	10.61	-1.51	3	.229	0.50	0.43
		CONTROL	5	4.60	9.18	1.12	4	.325	0.09	0.08
	B-F	CASE	4	-10.50	9.04	-2.32	3	.103	0.54	0.47
		CONTROL	5	0.20	5.67	0.079	4	.941	0.00	0.00
ACS	B-E	CASE	4	5.75	20.30	.566	3	.611	0.27	0.24
		CONTROL	5	7.60	21.92	0.78	4	.481	0.17	-0.15
	B-F	CASE	4	12.00	20.75	1.15	3	.331	0.40	0.35
		CONTROL	5	-0.40	20.47	-0.044	4	.967	0.14	0.12
PCL-M	B-E	CASE	4	-6.25	4.71	-2.65	3	.077∇	0.49	-0.42
		CONTROL	5	-0.50	9.58	-0.12	4	.913	0.17	0.15
	B-F	CASE	4	-2.25	5.38	-0.83	3	.464	0.19	-0.17
		CONTROL	5	0.50	4.18	0.27	4	.802	0.32	0.28
WHOQOL	B-E	CASE	4	-4.00	7.62	-1.05	3	.371	0.28	0.25
		CONTROL	4	-2.88	3.12	-1.84	3	.162	0.31	0.27

Note. E=endpoint, B=baseline, F=follow-up. M=mean difference, SD=standard deviation of the mean difference. Effect sizes (*d* and *g*) listed in the CONTROL rows were calculated based upon the difference between case and control groups at endpoint or follow-up. **p<0.01; *p<0.05. ∇trending result (0.05<p<0.1)

Table 11

Paired t-test Results for Mood and Sleep Item Scores on the DVPRS and BPI

			n	M	SD	t	df	p	d	g
DVPRS (mood)	B-E	CASE	4	3.25	0.96	6.79	3	.007**	1.33	1.16
		CONTROL	5	0.40	1.14	0.78	4	.477	0.08	0.07
	B-F	CASE	4	3.25	1.50	4.33	3	.023*	1.51	1.31
		CONTROL	5	0.40	2.07	0.43	4	.688	0.05	0.04
BPI (mood)	B-E	CASE	4	2.75	1.50	3.67	3	.035*	1.16	1.01
		CONTROL	5	-0.40	2.19	0.41	4	.704	0.11	0.10
	B-F	CASE	4	2.75	0.50	11.00	3	.002**	1.33	1.15
		CONTROL	5	0.40	1.14	0.78	4	.477	0.18	0.16
DVPRS (sleep)	B-E	CASE	4	3.50	1.91	3.66	3	.035*	1.37	1.19
		CONTROL	5	0.60	2.07	0.65	4	.553	0.80	0.71
	B-F	CASE	4	1.75	0.96	3.66	3	.035*	0.71	0.61
		CONTROL	5	-0.60	0.89	-1.50	4	.208	0.72	0.64
BPI (sleep)	B-E	CASE	4	2.50	1.92	2.61	3	.080∇	0.98	0.85
		CONTROL	5	0.20	3.42	0.13	4	.902	0.49	0.44
	B-F	CASE	4	1.25	1.26	1.99	3	.141	0.53	0.46
		CONTROL	5	0.20	2.78	0.16	4	.880	0.12	0.10

Note. E=endpoint, B=baseline, F=follow-up. M=mean difference, SD=standard deviation of the mean difference. Effect sizes (*d* and *g*) listed in the CONTROL rows were calculated based upon the difference between case and control groups at endpoint or follow-up. **p<0.01; *p<0.05. ∇trending result (0.05<p<0.1)

Cognitive Functioning

For the CPT II, case group participants improved in vigilance, the ability to sustain reaction time over the duration of the test. Vigilance is quantified by Hit Reaction Time by Block (HRB), the change in reaction time across subsequent blocks of the test. Significance was detected from B-E for both the main effect of time, $F(1,7)=14.49$, $p=.004$, $\eta^2=.218$ and interaction of time and group, $F(1,7)=22.29$, $p=.002$, $\eta^2=.278$. Values for HRB decreased from baseline ($M=53.81$, $SD=3.62$) to endpoint ($M=41.56$, $SD=2.31$) in the case group, indicating that participant responses became faster as the test progressed. This difference in HRB was significant for the case group, $t(3) = 9.95$, $p=.002$ as compared to no change for the control group, $t(4) = -0.332$, $p=.757$. No other measure on the CPT II (inattention, impulsivity) was found to be significant.

Patient Impression of Change

Perceived improvements in activity limitations, symptoms, emotions, and overall quality of life were found among case group participants. Mean responses on the PGIC 7-item scale at endpoint ($M=5.50$, $SD=0.58$) and follow-up ($M=5.50$, $SD=0.58$) indicate that participants responded on average between a '5' ('moderately better, a slight but noticeable change') or '6' ('better, a definite improvement that has made a real and worthwhile difference). In contrast, the mean control group response was a '2' ('almost the same, hardly any change at all') at endpoint ($M=2.20$, $SD=1.30$) and follow-up ($M=2.00$, $SD=1.00$). An independent samples t-test confirmed that the differences between groups were significant at endpoint, $t(7) = 4.66$, $p=.002$ and at follow-up, $t(7) = 6.17$, $p=.000$.

Similar results were found for the PGIC 11-point NRS. The mean response to the degree of change was between a '0' ('much better') and '5' ('no change') at endpoint ($M=2.25$, $SD=0.96$) and at follow-up ($M=3.37$, $SD=2.50$) for the case group. Control group responses corresponded to 'no change' at endpoint ($M=5.60$, $SD=1.14$) and follow-up ($M=5.40$, $SD=1.14$). These differences between case and control groups were significant at endpoint, $t(7) = -4.68$, $p=.002$, but not at follow-up, $t(7) = -1.63$, $p=.146$.

Clinical Pain Evaluations revealed that 54% of reported pain areas by case group patients at baseline were either 'greatly improved' (n=3) or 'moderately improved' (n=3) at endpoint. In contrast, 50% of pain areas were "moderately worse" (n=5) or 'greatly worse' (n=1) among control group

participants (Figure 21). Patients reporting their pain area to be the 'same' were 27% (n=3) and 42%

(n=5) for the case and control groups, respectively.

When provided a list of symptoms and asked if they noticed any improvement since the beginning

of the study, case group participants identified trouble sleeping, headaches, energy level, irritability/angry

outbursts, depression, anxiety, and concentration—as 'yes somewhat' improved or 'yes completely'

improved at endpoint (Figure 22). These reported improvements were maintained or enhanced at follow-

up except for anxiety (Figure 23). In comparison, a larger proportion of control group participants

responded 'no' improvement on most symptoms except for depression and upset stomach at endpoint

(Figure 24). Notably back pain, musculoskeletal pain, and headaches were largely not improved in the

control group at baseline and follow-up (Figures 24-25) as compared with higher percentages of

improvement in the case group for these pain symptoms (Figures 22-23). Participants who responded

'Don't' have this problem' for a given symptom were not included in the bar graph for that particular

symptom in Figures 22-25.
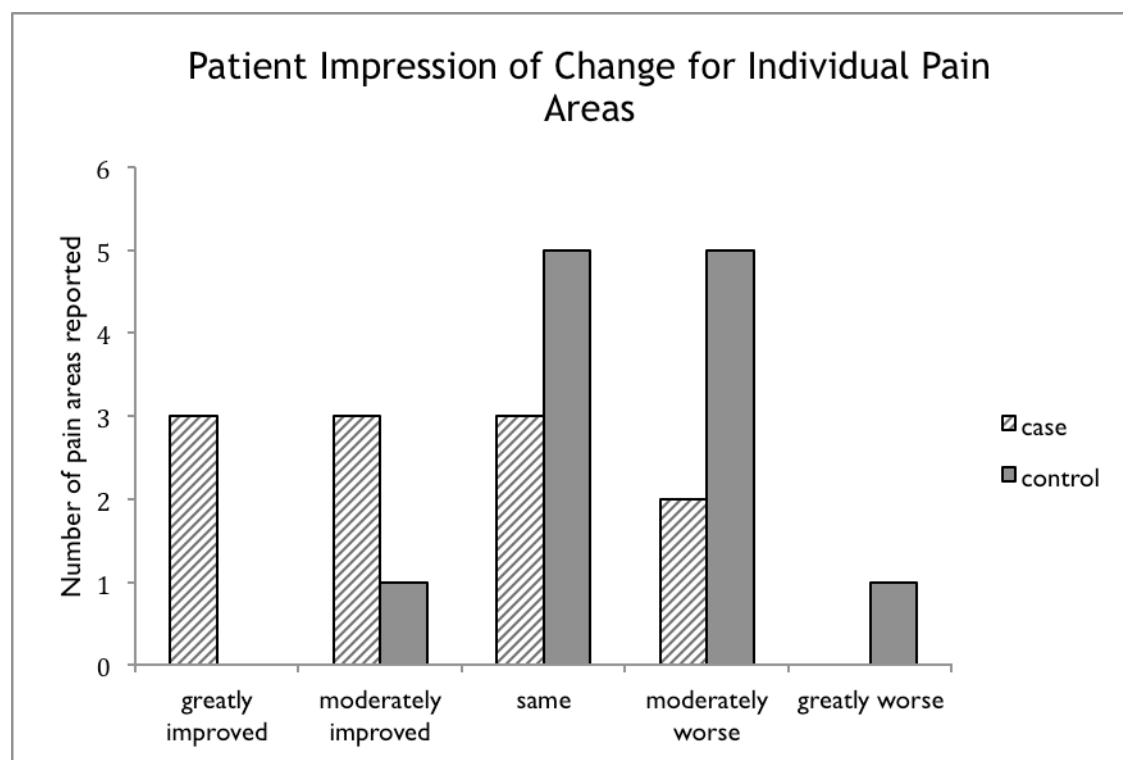
Figure 21. Impression of Change for Individual Pain Areas Verbally Reported During the
Clinical Pain Evaluation.
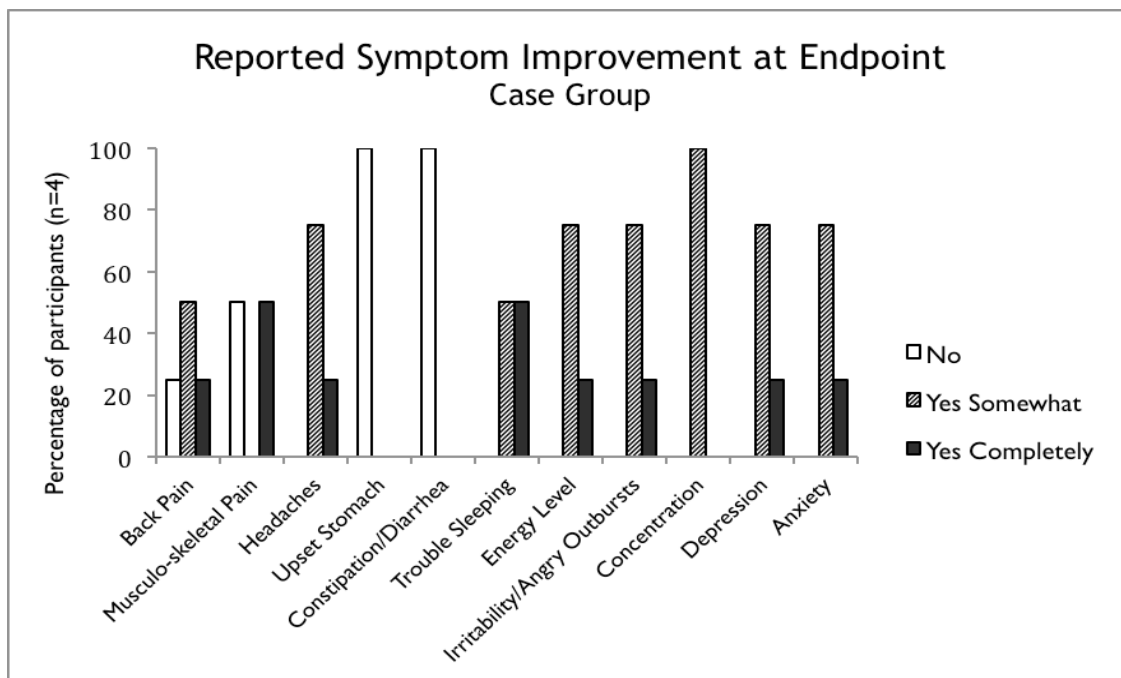
Figure 22. Case Group Responses at Endpoint to the Question, "Since beginning this study, have you noticed any improvements in the following symptoms?"
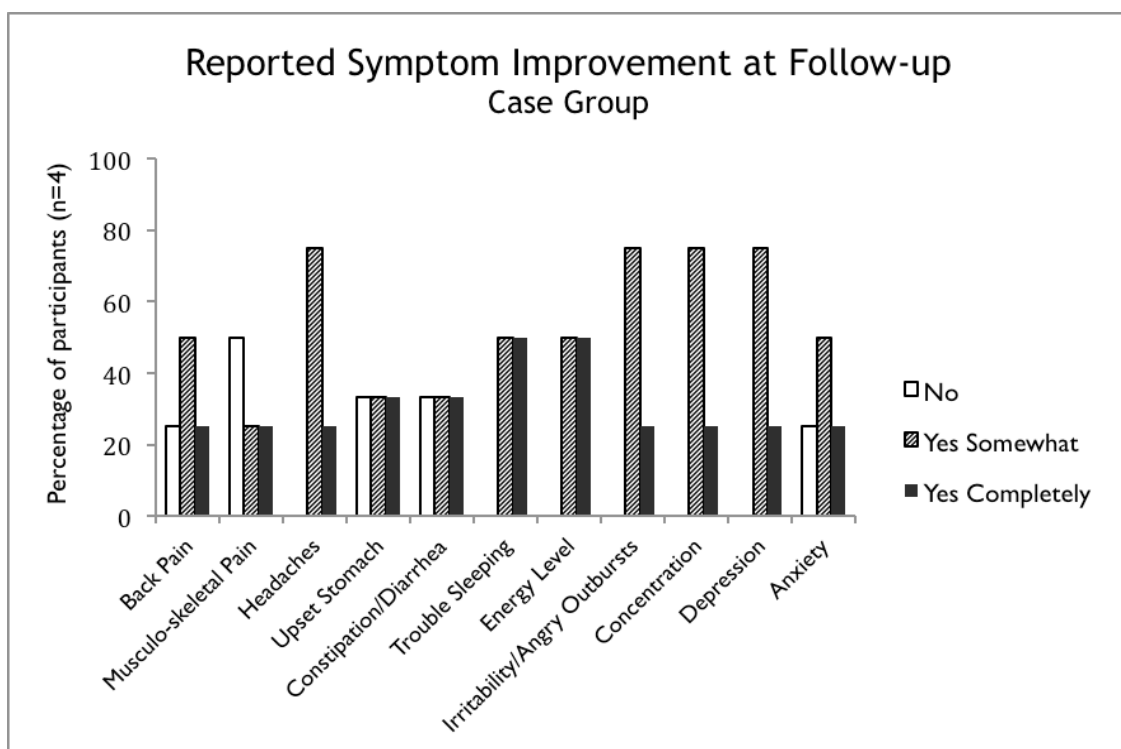
Figure 23. Case Group Responses at Follow-up to the Question, "Since beginning this study, have you noticed any improvements in the following symptoms?"
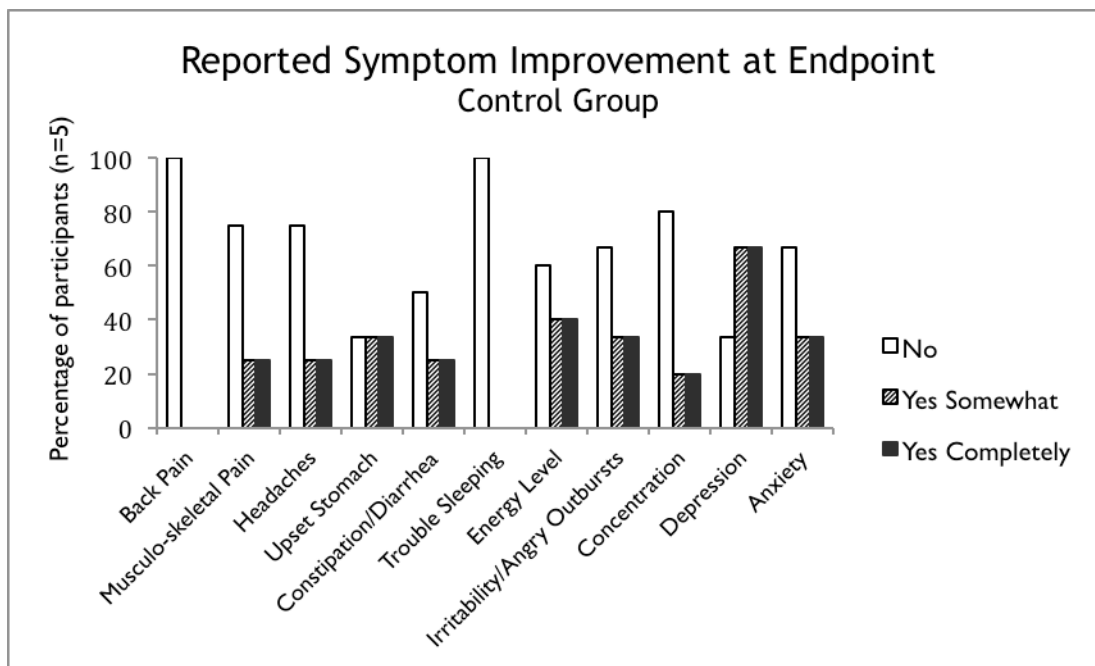
Figure 24. Control Group Responses at Endpoint to the Question, "Since beginning this study, have you noticed any improvements in the following symptoms?"
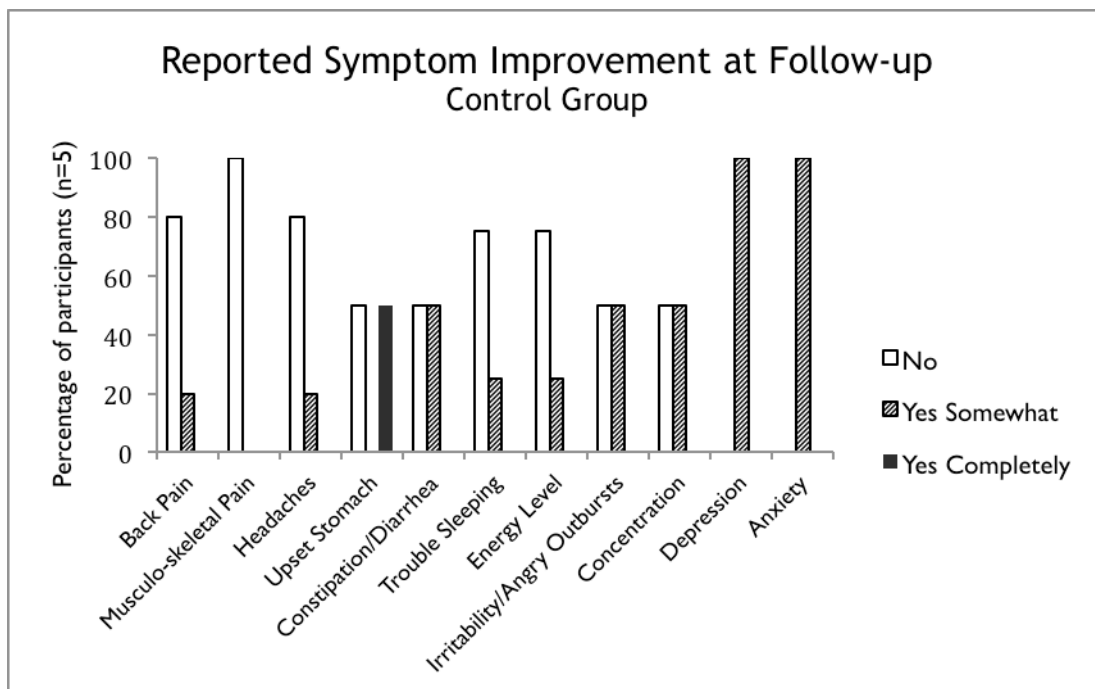
Figure 25. Control Group Responses at Follow-up to the Question, "Since beginning this study, have you noticed any improvements in the following symptoms?"

Collectively, the percentage of patients responding 'yes completely' or 'yes somewhat' to any symptom on the PGIC at endpoint was 86% for the case group compared to 30% in the control group and these differences between groups were mainly sustained at follow-up (Figure 26). Chi-square analyses indicated that symptom improvement ('yes completely,' 'yes somewhat,' 'no') was strongly associated with group membership (case, control) at endpoint, X^2(2, N=80) = 26.25, p=.00, Cramer's V=.573, and at follow-up, X^2(2, N=79) = 24.32, p=.00, Cramer's V=.555. A significant association between symptom improvement and group was maintained when 'yes completely' and 'yes somewhat' were combined into a single category ('yes,' 'no') at endpoint, X^2(1, N=80) = 25.57, p=.00, Cramer's V=.565, and at follow-up, X^2(1, N=79) = 21.37, p=.00, Cramer's V=.520.
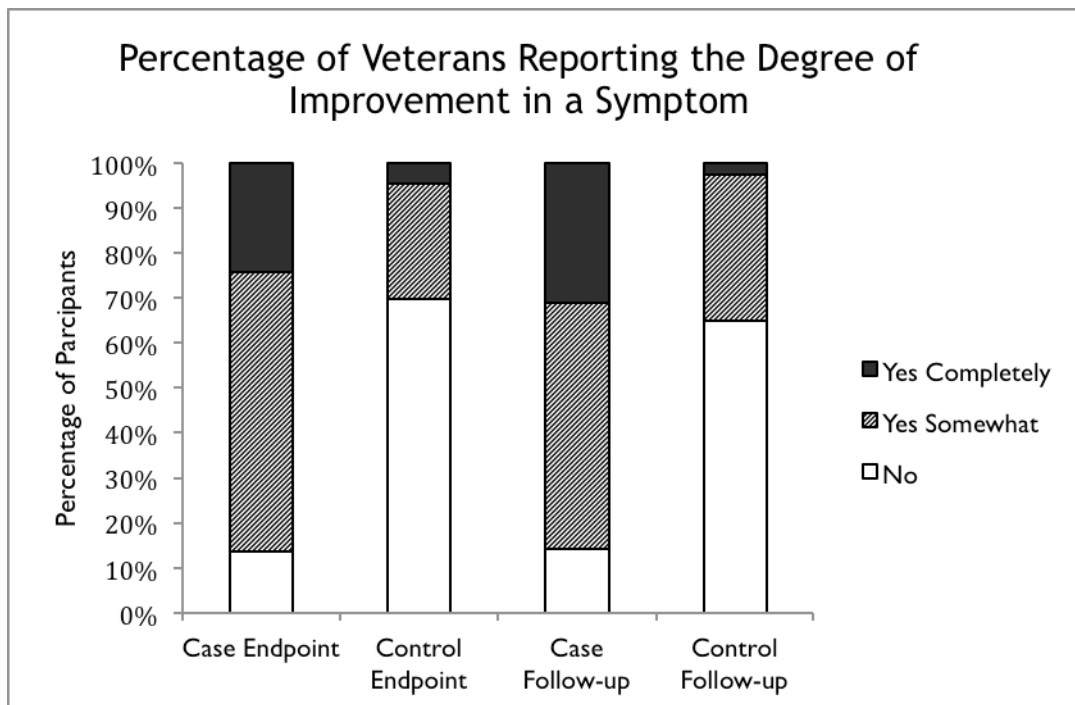
Figure 26. Percentage of Patient Responses to All Symptoms on the PGIC (Back Pain, Musculoskeletal Pain, Headaches, Upset Stomach, Constipation/diarrhea, Trouble Sleeping, Energy Level, Irritability/angry Outbursts, Concentration, Depression, and Anxiety).

Table 12 presents the oral comments made by individual participants during the formal iRest sessions, arranged into clusters of common themes. Patients frequently cited the following as being most affected by iRest practice: 1) duration, initiation, and quality of sleep, and 2) emotional regulation relative to pain relief and response to stressors (Table 12).

Table 12

Comments made by Individual Participants during Formal iRest Sessions Arranged into Clusters of Common Themes

---

Sleep
  1. Duration of sleep
      a. He was able to sleep after the first class for 3 straight hours, a big accomplishment for him.
      b. The Veteran sleeps longer when he listens to iRest before bed, almost like going into a deep sleep which is a place he hardly ever experiences.
      c. His sleep has improved to 4 hours per night, where 2 ½ hours has been the norm for him.
      d. He is sleeping 5 hours a night without waking, more than doubling the amount of sleep compared to when the study began.
      e. At 10 pm he was lying on the couch listening to iRest and slept until 4am. He got up and went back to sleep in his bed until 9:30pm, the most sleep he has had in 2 weeks.
      f. The amount of sleep he gets on a typical night is 5-6 hours, 3 times longer than from the beginning of the study, and wakes with no pain.

  2. Initiation and quality of sleep
      a. Some days he listens to iRest twice during the day as doing so makes it easier to fall asleep.
      b. He practices iRest daily at bedtime and usually falls asleep during his self-practice.
      c. He has been using the practice for sleep when he cannot fall asleep at night. He is hesitant to do the practice during the day as he does not want to fall asleep because he is concerned it will further interfere with his ability to sleep at night.
      d. The patient uses the home practice to help him sleep when he returns home from work and cannot get to sleep.
      e. He listens to the iRest recordings daily at night to sleep.
      f. The patient continues to feel that the practice is of benefit to sleep.
      g. When he puts on the recording he sleeps through the night to the next morning.
      h. Even if he does not sleep during the night, listening to the iRest practice makes him feel rested the next day. Last night he slept 3 ½ hours, one of the best sleeps he has had.
      i. The practice is most effective when he stays awake instead of falling asleep, like when he attends the formal iRest sessions; he feels more relaxed and this effect lasts the entire day.

Table 12 (continued)

Comments made by Individual Participants during Formal iRest Sessions Arranged into Clusters of Common Themes

---

Emotional Regulation
  3. Pain relief
      a. He began the iRest session feeling very bad but did not want to mention it. By the end, his headache was gone and he was surprised that he felt such an immediate positive response.
      b. The patient is feeling calmer, and his pain is less prevalent
      c. The participant feels less stressed and his pain level has dropped.
      d. While relaxing and meditating he is able to find peace and to also feel less pain.
      e. Overall, the practice has helped his sense of ease in the world and his physical pain. The pain is still present, but it has shifted to the background.
      f. When he tries to fight the pain in his back, it gets much worse and shoots to his leg. With iRest he learned to let go and relax, instead of fighting the pain. The pain is still there, but when he listens to the practice and relaxes, the pain does not spread from his back.
      g. He finds the concept of welcoming difficult experiences like pain to be challenging.

  4. Response to stressors
      a. The patient used to be scared with the thought of not waking up. A lot of 'crazy ideas' would pass through his mind. He also felt that he could not let himself go into a deep sleep. But since beginning his practice of iRest, he no longer worries about waking up.
      b. Things do not bother him as much. He feels that he is able to pause before reacting to a situation and that he is not as argumentative.
      c. The participant is not as wound up as he used to be. Instead of being primed to react, now he walks away from challenging situations in which he used to overreact.
      d. Someone hit his car bumper in the parking lot and he laughed. Before iRest, he would have gotten out of his car and broken the person's windshield. Today he simply walked away.
      e. Before, he had been on pins and needles in response to stressful events in his life. Now he is learning what he can and cannot control.
      f. He feels calmer in general and more able to discern what he needs to respond to, in that his sense of being on guard all the time is lessening. He sees more clearly what requires a response in the moment and what is unnecessary over activation of his nervous system
      g. He used to isolate himself off from the world while paying very close attention to everything that looked like a potential threat. He is now more able to differentiate between potential dangers that need to be paid attention to, and what he can let go of.
      h. He is not as 'jumpy' and has a sense of a safe place. The bad days are not as bad, and the bad things do not last as long
      i. He reports feeling more relaxed even in the face of several stressors in the family.
      j. With iRest he does not have as much anxiety or as many issues with trust.
      k. His inner resource has permeated his dreams and he finds himself dreaming of being at the beach. His sense of hyper-vigilance is also diminishing.
      l. iRest helps him to cope more, to experience love, peace and more love rather than hate.
      m. Through iRest he is willing to find a better, more peaceful place than hate and negativity.
      n. The tactical military environment is black and white, but iRest helps him to begin to see the shades of gray, so that there are more options to respond.
      o. His mind was numb when finding out he would need to have surgery, and a close family member of his was in a coma. Normally his blood pressure rises, he gets nose bleeds, and he takes his frustration out on those around him. But this time, his nose did not bleed and he felt much more calm and relaxed, even after receiving the bad news.
      p. He finds it challenging to work with the emotions in the practice. It feels especially hard to stay with strong emotions like anger.

Biochemical Measures

Table 13 provides baseline and endpoint biochemical measures among individual participants for urinary free cortisol (UFC), creatinine, total urine volume, UFC per concomitant creatinine (UFCC), UFCC per BMI and serum interleukin-6 (IL-6). One control participant was removed from the biochemical analysis due to inadequate urine collections. Thus, four control and four case participants were included in the biochemical analysis. BMI was negatively correlated with UFCC across baseline and endpoint measurements for all participants , $r=-.595$, $N=16$, $p=.015$. A trending positive correlation was found between IL-6 and pain intensity on the VAS, $r=.492$, $N=16$, $p=.053$. Mean UFCC and IL-6 for case and control groups at baseline and endpoint are shown in Figures 27 and 28. An independent samples t-test confirmed that the between group differences at baseline was significant for UFCC, $t(6) = -2.75$, $p=.033$, but not for IL-6, $t(6) = .34$, $p=.75$. Paired samples t-tests revealed that B-E differences for UFCC and IL-6 were nonsignificant for the case group, $t(3) = -2.00$, $p=.14$, $t(3) =.815$, $p=.48$, and control group, $t(3) = 1.66$, $p=.20$, $t(3) = -1.49$, $p=.23$. No relationship was observed between IL-6 and UFCC measures at baseline, $r=-.171$, $N=8$, $p=.69$, or endpoint, $r=-.444$, $N=8$, $p=.27$.

Table 13

Biochemical and Body Composition Measures

		BMI	UFC	Crt	Volume	UFC/Crt	(UFC/Crt)/BMI	IL-6
Case Participants	B	30-34	13.0	1.61	1800	8.07	0.27	0.91
	E		30.6	3.13	1200	9.78	0.32	0.37
	B	30-34	17.3	3.35	3000	5.16	0.17	0.47
	E		18.1	2.31	3300	7.84	0.26	0.84
	B	30-34	8.3	1.47	900	5.65	0.18	1.14
	E		13.9	2.25	700	6.18	0.20	0.23
	B	35-40	17.1	5.04	2600	3.39	0.09	0.45
	E		15.0	4.49	1200	3.34	0.09	0.57
Control Participants	B	25-29	62.5	2.15	1600	29.07	1.02	0.41
	E		31.4	2.59	1800	12.12	0.43	1.02
	B	25-29	23.1	1.65	750	14.00	0.52	1.02
	E		24.4	2.20	725	11.09	0.41	0.55
	B	25-29	24.3	1.26	2300	19.29	0.69	0.76
	E		35.2	2.50	900	14.08	0.50	1.54
	B	35-40	21.6	2.47	3000	8.74	0.25	0.48
	E		24.8	2.78	2900	8.92	0.26	1.92

Note. B=baseline, E=endpoint, BMI = body mass index, UFC = urinary free cortisol, Crt = creatinine, Volume = total volume of urine excreted over 24 hours, IL-6 = interleukin-6. Units of measurement are as follows: BMI = kg/m^2, UFC = mcg/24hours, Creatinine = g/24 hours, Volume = mL, IL-6 = pg/mL. Reference Ranges: UFC = 4.0-50.0 mcg/24 hours; Creatinine = 0.63-2.50 g/24 hours; IL-6 = 0.447-9.96 pg/mL.
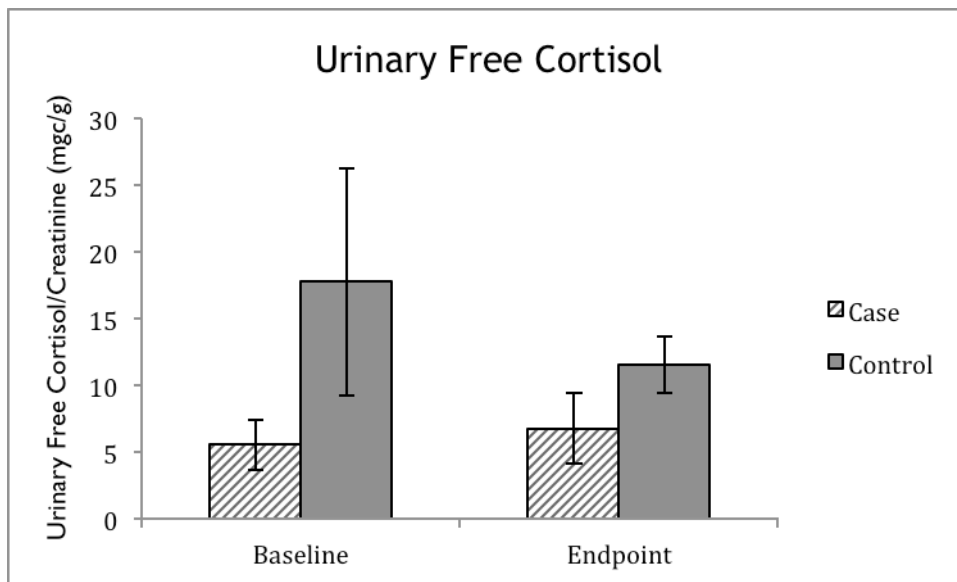
Figure 27. Urinary Cortisol Excretion Over 24 Hours from Baseline to Endpoint.
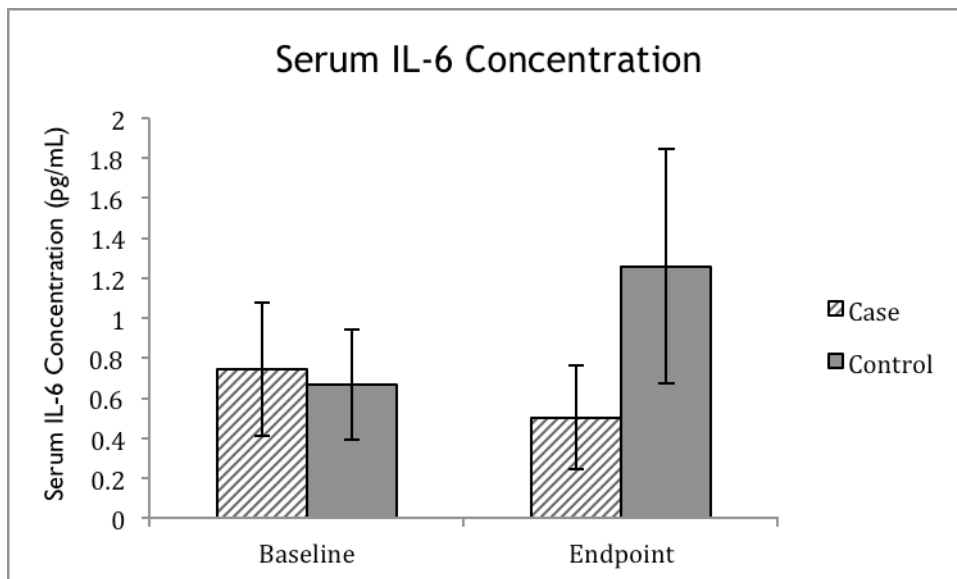
Figure 28. Serum Interleukin-6 (IL-6) Concentration from Baseline to Endpoint.

CHAPTER 4

DISCUSSION

The results of the present study offer tentative support for the primary hypothesis that an 8-week iRest program would achieve minimally important changes in pain intensity and pain interference, as defined by IMMPACT. Veterans receiving iRest reported at least a 20% reduction in pain intensity and pain interference on average for all primary outcome measures and time points examined, with the exception of BPI pain severity from baseline to follow-up. In comparison, the control group never reached a 20% average decrease for pain intensity or interference on any outcome measure (Table 5). The consistency of these findings across different pain instruments (VAS, DVPRS, BPI) offer further evidence for the potential effectiveness of iRest for managing chronic pain in a combat Veteran cohort.

Pain Intensity and Interference

The current results are consistent with other controlled studies that have employed similar mindfulness meditation techniques for chronic pain patients (Baird et al., 2004; Reiner et al., 2013; Veehof et al., 2011). According to the meta-analysis by Reiner et al. 6 out of 8 controlled studies also reported significantly greater decreases in pain intensity for the mindfulness-based intervention group. The range in reported pain intensity reductions across studies (11.8% – 49.4%) was comparable to the results obtained from the different pain measures used in the present study (9.43% – 42.44%; Table 5). Additionally, effect sizes (g) for pain intensity were primarily of small to medium size in the controlled studies reported by Reiner et al. (0.29 – 0.64) and Veehof et al. (0.37; 95% CI: 0.20 – 0.53), which are comparable with those observed between groups at endpoint and follow-up in this study (0.37 – 0.61; Table 7).

However, most studies employed pain intensity as the primary outcome measure, which may explain why larger effect sizes were not found. Veehof et al. (2011) contends that pain interference may be a more suitable means for assessment in this area of research, due to the emphasis of mindfulness interventions on acceptance. In this study the case group demonstrated substantial decreases in pain interference across time points and measures (32.72% – 41.06%; Table 5). These reductions were accompanied by large effect sizes within the case group from B-E (0.92 – 1.05) and B-F (0.95 – 1.13;

Table 7). In comparison, the control group did not reach clinical significance across measures and time points (<10%; Table 5). Nonetheless, these findings must be approached with caution since mean pain interference was 22 – 25% lower among controls at baseline compared to the case group.

<div align="center">
Depression and Interference of Pain with
Mood and Sleep
</div>

The case group also achieved clinically important reductions in depressive symptoms as defined by IMMPACT (Dworkin et al., 2008) and BDI-II guidelines (Beck et al., 1996), from moderate depression at baseline (*M*=25.50) to mild depression at endpoint (*M*=18.75). These findings were further validated by the significant decreases in interference of pain on mood, which were consistent across measures (BPI and DVPRS) and time points (Table 11). Because depressive symptoms tend to worsen as pain severity increases (Carroll et al. 2000; Moldin et al., 1993), mindfulness meditation-induced improvements in depression could reduce pain intensity and interference. Veehof et al. (2011) cited small to moderate effect sizes for both depression and pain intensity among studies involving acceptance-based interventions on chronic pain patients. In the current study, effect sizes for depression within the case group were moderate to large (0.59 – 0.83; Table 10). Although no significant difference in mean BDI-II scores was detected for the control group (Table 10), these participants began the study with a clinically lower mean score (*M*=16.60) compared to the case group (*M*=25.50). As with pain interference, a floor effect is possible. However none of the control participants, including those with self-reported moderate and severe depression at baseline, demonstrated an improvement in diagnostic criteria (i.e. from moderate to mild or from severe to moderate) at endpoint. In contrast, all but 1 participant in the case group reported clinically significant improvements in depression. This patient incidentally reported the lowest frequency of iRest self-practice among case group participants, suggesting a possible dose effect. Yet, similar to pain interference, the disparity of measurements at baseline preclude definitive conclusions regarding the apparent improvements in depression.

Depression has been suggested to be a significant contributor to increased pain severity and sleep disturbance among Veteran outpatients (Chapman et al., 2006). In parallel with the mood subscale for pain interference, case group participants reported decreased interference of pain with sleep at endpoint and follow-up according to DVPRS scores. But sleep findings were mixed for the BPI, trending

towards decreased interference from B-E and non-significant from B-F. An examination of individual data reveals that the interference ratings were numerically lower from B-E and B-F for 3 of the 4 case group participants, with 1 participant reporting the same interference at all time points. Qualitative data also appear to support the claim that Veterans experienced improved sleep in response to iRest. Comments voiced by the case group during the formal iRest sessions revealed that sleep duration (clusters 1a-1f), initiation (2a-2e), and quality (1b; 2f-2i; 4a) appeared to be enhanced among individual participants (Table 12). One Veteran reported that he "sleeps longer when he listens to iRest before bed, almost like going into a deep sleep which is a place he hardly ever experiences" (1b). According to reports from another participant, improved sleep and pain were associated: "the amount of sleep he gets on a typical night is 5-6 hours, 3 times longer than from the beginning of the study, and wakes with no pain" (1f). It is possible that any progress made towards enhanced sleep was somewhat diminished following the completion of the formal iRest sessions at endpoint, after which point fewer benefits were received from the practice in relation to pain interference with sleep.

<u>Emotional Regulation, Pain Relief and Effective</u>
<u>Responding to Stressors</u>

iRest participants reported improved emotional regulation, which appear to mediate pain relief (3a-3f; Table 12). For some Veterans the practice led to a temporary reprieve from pain, "While relaxing and meditating I am able to find peace and also feel less pain" (3d), whereas in others the pain seemed to become less unpleasant, "Overall, iRest has helped my sense of ease in the world and my physical pain. The pain is still there, but it has moved to the background" (3e). In another patient, strong emotions seemed to exacerbate his experience of pain: "When I try fighting the pain in my back, it gets much worse and shoots up my leg. With iRest I learned to let go and relax instead of fighting the pain. The pain is still there, but when I listen to the voice and relax, the pain doesn't spread from my back" (3f).

Case group participants also emphasized their enhanced ability to respond to stressors more effectively and constructively (4a-4o): "Before, I had been on pins and needles in response to stressful things in my life. Now I am learning what I can and can't control" (4e). "Things don't bother me as much. I feel like I am able to pause before reacting to a situation and I end up not being as argumentative" (4b). For one Veteran, fear of falling asleep and not returning to a waking state was a significant stressor, "I

used to be scared with the thought of not waking up. A lot of crazy ideas would pass through my mind. I also felt like I could not let myself go there, into that deep sleep. But since I began doing iRest, I no longer worry about waking up" (4a).

Finally, one participant described his improved physiological response to stress,

> "My mind was numb when I found out I needed to have surgery, and a close family member was in a coma. Normally my blood pressure rises, and I get nose bleeds, and take out my frustration out on everyone around me. But this time, my nose didn't bleed and I felt much more calm and relaxed, even after hearing the bad news" (4o).

Despite these reported improvements in emotional regulation, no differences were detected for symptoms of PTSD (PCL-M) or the ability to manage fear of strong emotions (ACS). Case group Veterans on average met criteria for PTSD at baseline (M=43) according to cut-offs suggested by VHA guidelines (Department of Veterans Affairs, 2013). These participants trended towards a worsening in PTSD symptoms at endpoint (M=49.25). Although all case group patients had numerically higher PCL-M scores from B-E, only 2 of the 4 participants would be considered as having a minimally "reliable change" (>5) in PTSD symptoms according Department of Veterans Affairs National Center for PTSD (2013). In comparison, control participants were clinically higher on the PCL-M at baseline (M=51.9), but remained closely within this range at endpoint (M=52.4) and follow-up (M=51.4). These findings are in contrast to two uncontrolled iRest studies on active duty military patients (Engel) and Vietnam-era combat Veterans (Stankovic, 2011), which respectively found decreasing trends in PTSD and emotional reactivity. One possible explanation for the slight worsening in PTSD symptoms is that iRest, unlike many other forms of mindfulness meditation, encourages participants to witness difficult emotions and work with them until they begin to subside and lessen in strength. Although case participants may have observed some progress in their ability to regulate emotions in response to everyday stressors, perhaps a longer iRest intervention period is needed to achieve reductions in PTSD symptoms or particularly strong emotions associated with prior experiences in combat theater.

<u>Mindfulness, Sustained Attention
and Reaction Time</u>

Mindfulness scores on the FFMQ as a whole did not significantly differ for either group. However, all case participants demonstrated B-F improvements in Act with Awareness, a subscale of the FFMQ that pertains to maintaining focus and sustaining attention on tasks in the present moment without becoming distracted. Vigilance, the ability to sustain attention on the CPT II, also improved in the case group from B-E. In particular, case group Veterans demonstrated progressively faster reaction times across subsequent blocks of the CPT II during endpoint administration as compared to baseline. Relative to normative ranges for the CPT II, baseline performance was "mildly atypical" for 1 case participant and "within the average range" for the other 3 patients. At endpoint, all case participants significantly improved in vigilance, achieving a "good performance." All control group performances were "within the average range" at baseline and endpoint except for 1 participant who was "mildly atypical" at baseline. No significant differences in mindfulness or cognitive performance were found for the control group.

These findings are in agreement with other studies that have verified the beneficial effects of mindfulness meditation on sustained attention and reaction time (Lutz et al., 2009; Moore & Malinowski, 2009; Valentine & Sweet, 1999; Zeidan, Gordon, et al., 2010). Because mindfulness meditation cultivates a balance between relaxation and vigilance (Wallace, 2006), it is plausible that enhanced cognitive performance could be mediated by the calming attributes of mindfulness practice coupled with the heightened ability to focus on the present moment (Zeidan, Johnson, et al., 2010).

Developing the ability to self-regulate emotions has also been shown to be a vital factor in augmenting cognition (Austin, 1998; Moore & Malinowski, 2009). By teaching participants to acknowledge potential distractors such as feelings, thoughts, and emotions, while continually shifting attention back to the techniques of the practice, mindfulness meditation may nurture present moment awareness (Zeidan, Johnson, et al., 2010) and develop attentional stability (Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009; Wallace, 2006). Mind-wandering in particular has been shown to negatively impact cognitive performance by diminishing control over goal-directed attention (Smallwood, McSpadden, & Schooler, 2007). Whereas negative mood may result in rumination and deficits in attention, improved mood may lessen mind-wandering (Smallwood, Fitzgerald, Miles, & Phillips, 2009; Zeidan, Johnson, et

al., 2010). Therefore, in the current study it is possible that case participants' reports of improved

depressive symptoms (BDI), mood (DVPRS and BPI), and emotional regulation (qualitative data) may

partly account for the improvements in sustained attention on the CPT II.

<div align="center">Global Impression of Change</div>

At endpoint and follow-up, case group participants reported on the PGIC 7-item scale that their

activity limitations, symptoms, emotions, and overall quality of life related to their painful condition were

'moderately better, a slight but noticeable change'' or 'better, a definite improvement that has made a real

and worthwhile difference' in response to the 8-week iRest program. Additionally, the mean case group

response to the degree of change since the beginning of the study on the PGIC 11-point NRS was

between 'much better' (highest score possible) and ''no change' for the case group. The perceived

improvements in activity limitations and symptoms and the overall degree of change were reflected by the

Clinical Pain Evaluations, which revealed that 54% of reported pain areas by case group patients at

baseline were either 'greatly improved' or 'moderately improved' at endpoint. These findings were also

aligned with individual reports that trouble sleeping, headaches, energy level, irritability/angry outbursts,

depression, and concentration were 'somewhat' improved or 'completely' improved at endpoint and

follow-up (Figures 22-23).

However, not all case group participants reported improved symptoms. At follow-up, one Veteran

expressed concern about an upcoming surgery on his cervical spine to remedy the loss of function in his

left arm. From his perspective, the iRest practices of body sensing and progressive muscle relaxation

made him aware of a distinct sensation of numbness in his left shoulder. The patient further noticed that

he had less range of motion in his left arm when compared to the right: "I went to the doctor to get

checked out and they discovered that there was no cartilage between two of the discs in my spine. I had

probably had this issue for years, but just now became aware of it." A possible benefit of mindfulness

meditation may be heightened somatic awareness of impending bodily injury and disease that need to be

addressed in order to maintain health and avoid further damage or harm.

In contrast to the case group, mean control group responses were 'almost the same, hardly any

change at all' for the PGIC 7-item scale and 'no change' for the PGIC 11-point NRS. These findings were

<div align="center">71</div>

consistent with control reports that 50% of pain areas were "moderately worse" or 'greatly worse' and 42% were the 'same' (Figure 21). Collectively, the percentage of patients responding 'yes completely' or 'yes somewhat' to any symptom on the PGIC at endpoint was only 30% in the control group compared to 86% for the case group (Figure 26).

However, quality of life according the WHOQOL-BREF was nonsignificant for both groups. One possible explanation is that this measure evaluates broad facets of life improvement (i.e. social relations, environment, level of independence, spirituality) that may not necessarily be expected to change over the course of an 8-week period. The PGIC assessments were far more specific in scope, relating perceived improvements to their painful condition and associated symptoms.

<u>A Biopsychological Model of Mindfulness</u>
<u>Meditation and Pain</u>

Findings from this study illustrate the complex, subjective nature of pain, which cannot be easily quantified or objectively measured (Gatchel et al., 2007; Institute of Medicine, 2011). Although pain intensity is routinely evaluated using patient self-report measures such as the visual analog scale (VAS) and numeric rating scale (NRS), these assessments rely entirely on the individual's perceived severity of pain rather than the actual magnitude of nociceptive sensation. Thus, psychological factors may play a substantial role in determining and regulating an individual's experience with pain (Zeidan et al., 2012). Considerable cognitive, emotional and behavioral resources are devoted to self-regulation in humans (Gross, 1998), and even more so in chronic pain patients who must cope with the unrelenting, intense pain accompanying their condition (Solberg, 2009).

Mindfulness meditation encourages patients to sustain attention on pain sensations from a nonjudgmental perspective, without evoking the unpleasant cognitions or emotions that normally accompany nociceptive sensation (Reiner et al., 2012). Through acts of nonjudgmental observation and sustained awareness, mindfulness meditation has been theorized to separate the cognitive and emotional constituents of pain from the sensory component (Kabat-Zinn, 1982). This shift in how pain is perceived would reduce load on cognitive and emotional resources that were previously engaged with the chronic sensory pain accompanying nociception (Solberg, 2009). Prolonged mindful observation and awareness of chronic pain sensations could lead to desensitization, leading to lessened emotional reactivity and

pain-related distress over time (Baer, 2003). Teasdale (1999) and Teasdale et al. (1995) have suggested that the nonjudgmental, decentered perspective of cognitions elicited by mindfulness training may block ruminative thought patterns in depressive patients, and redirect attention to the present awareness (Baer, 2003). Enhanced self-observation from mindfulness training can heighten awareness of pain sensations as they arise, enabling patients to engage in coping responses, acquired from mindfulness practice (Kabat-Zinn, 1982).

By positively influencing the cognitive and affective components of pain, mindfulness meditation will also beneficially impact the perception of pain severity. However, reduced pain severity is not likely to be achieved by direct action on the particular nociceptors in the peripheral nervous system implicated in a particular musculoskeletal pain condition. A more plausible explanation is that mindfulness meditation lessens the impact of pain through central nervous system (CNS) processes that increase coping skills to manage stress, regulate muscle tension and spasms, and help the individual to minimize the extent to which pain interferes with daily functioning (general activity, sleep, mood, level of stress; Figure 29). By decreasing pain interference through elevated mood, better sleep quality, improved physical functioning and greater overall well being, top-down inhibitory control on pain pathways may be enhanced, thereby attenuating the perceived severity of pain. Ultimately, reduced interference of pain with mood, sleep and levels of stress would be expected to decrease cognitive and emotional load, allowing for greater adaptability and flexibility in regulating behaviors, thoughts, and emotions, which would help patients apply the coping skills acquired from mindfulness meditation to bring about improved health outcomes and wellness (Reiner et al., 2012).

A putative neural mechanism to substantiate the notion of top-down inhibitory control of pain perception involves the anterior cingulate cortex (ACC), a brain structure implicated in opioidergic pain modulation (Casey et al., 2000; Zubieta et al., 2001) and placebo analgesia (Petrovic & Ingvar, 2002; Amanzio & Benedetti, 1999). Activation of the ACC has been linked with acute and chronic pain conditions according to functional magnetic resonance imaging (fMRI) studies (Chen, 2008), and research supports a role for the ACC in human pain perception and in the encoding of the affective-emotional components of pain (deCharms et al., 2005). Mindfulness meditation has been associated with changes in ACC activity and corresponding decreases in pain. Zeidan et al. (2011) determined that 4

73

days of mindfulness training in healthy, novice meditators produced reductions in pain intensity and pain

unpleasantness of 40% and 57%, respectively in response to applied noxious thermal stimuli during

meditation compared to a rest condition. These meditation-induced decreases in pain intensity were

correlated with increased brain activation of the ACC, which the authors postulate to be involved in

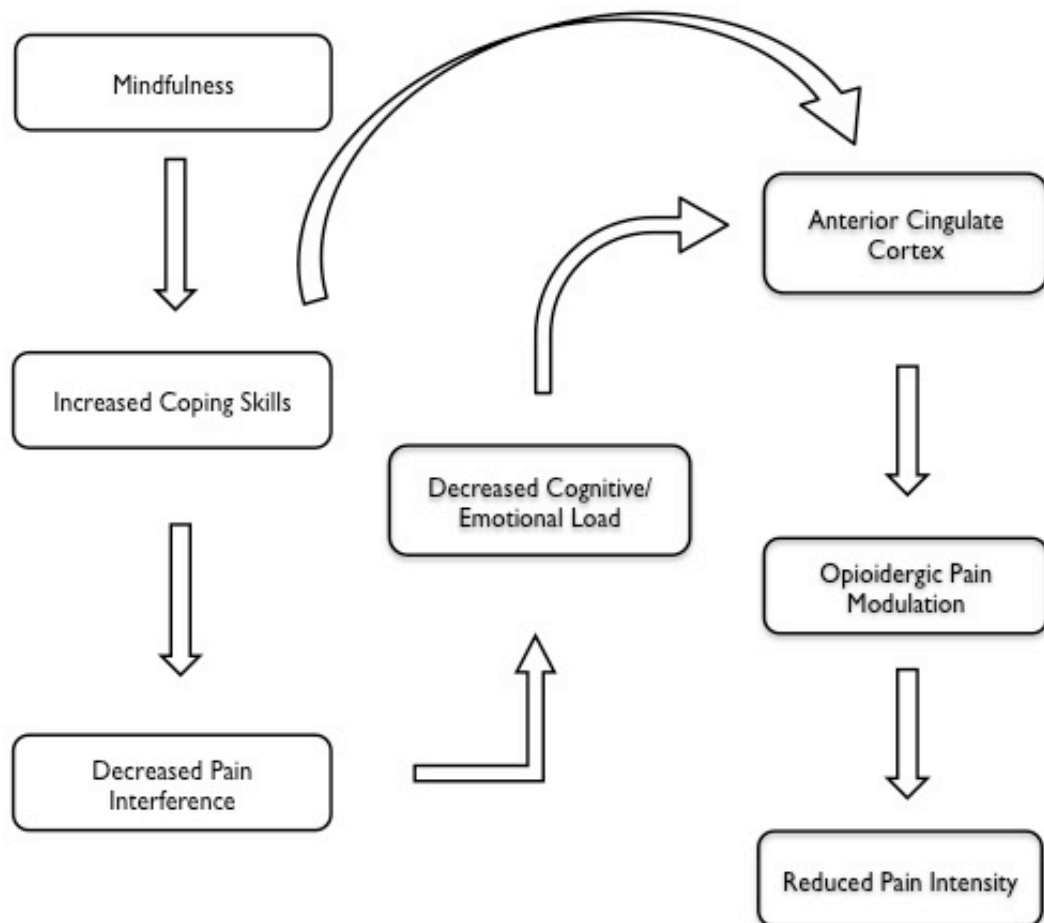cognitive regulation of nociceptive processing (Zeidan et al. 2011).

Figure 29. Proposed Biopsychological Model of Mindfulness and Pain Relief.

Intentional human control over ACC activation has been shown to influence pain perception. Using real-time fMRI (rtfMRI) training, deCharms et al. (2005) demonstrated that healthy subjects learned to control activation of the rostral ACC (rACC), as compared with four groups of participants assigned to experimentally robust control conditions. Further, when participants deliberately evoked increases or decreases in rACC fMRI activation, proportional changes in perceived pain resulted in response to experimentally-induced noxious stimuli. These findings were applied to chronic pain patients (in which no stimuli were applied) who were also shown to individually control rACC activation and their corresponding level of pain. Decreases in chronic pain continued to be found in these patients after the training. The authors contend that a trained, controllable form of the placebo effect explains the ability of participants to control their perception of pain (deCharms et al., 2005). Similarly, mindfulness meditation may serve as a cognizant form of placebo analgesia, in which practitioners engage in techniques acquired from mindfulness practice to reduce perceived severity of chronic pain.

<u>Biochemical Measures</u>

Urinary free cortisol per creatinine (UFCC) was elevated in the control group at baseline compared to the case group (Figure 27), which may be due to group differences in BMI. Of the 8 participants included in the biochemical analysis, 5 were obese (BMI$\geq$30) and 3 were overweight (BMI$\geq$25). All obese patients had distinctly lower UFCC levels (3.34 – 9.78 mcg/g) compared to the overweight patients (11.09 – 29.07 mcg/g) (Table 13). Because BMI was negatively correlated with UFCC for all participants and all 3 overweight participants were members of the control group, noticeable differences in UFCC were seen between groups at baseline. Recent studies have found serum cortisol to be negatively correlated with BMI in obese individuals (Travison et al., 2007) which may be an indication of adrenal insufficiency (Merton, Wardop, & Hadlow). In response to exercise, obese patients exhibit diminished cortisol release compared to healthy weight individuals (Sartorio et al., 2013), which might be due to chronically elevated cortisol levels over time, ultimately leading to a blunted stress response (Thomas et al., 2012). However, because this study performed urine rather than serum cortisol analysis, decisive statements cannot be drawn about the relationship between BMI and cortisol. Since all case group participants were obese (BMI$\geq$30) and began the study with lower cortisol levels, we would have

expected to see increased UFCC if iRest practice were to achieve a trend towards normalization. However, no differences were found from B-E. These findings are in contrast to two studies which had provided some evidence for the beneficial effects of meditation on cortisol levels (Kiran et al., 2005; Tang et al., 2010). Although IL-6 remained unchanged in case group participants from B-E, a trending positive correlation was found between IL-6 and pain intensity (VAS) across time points among all participants. But because significance was not achieved in correlations with other pain intensity measures (DVPRS, BPI), the link between IL-6 and the pathophysiology of pain (Wang et al., 2009) is tenuous based upon the results from this study. Nearly all measurements for IL-6 fell within the reference range (0.447-9.96 pg/mL), suggesting that participants exhibited normal circulating levels of this cytokine at both time points. Therefore it may have been unlikely to find changes in IL-6 at endpoint if case group participants exhibited baseline IL-6 measures within the normal range.

Study Limitations

Given that any research method has particular strengths and limitations, our approach was to research two of the most prevalent, highly comorbid health concerns in military and Veteran populations, chronic pain and TBI. However, there are several limitations to the current study that should be resolved in future research. Most importantly, the small sample size and low statistical power puts into question the validity of the statistical analyses. In an attempt to minimize the risk of Type I errors we purposefully selected a comprehensive analytical plan that systematically employed mixed ANOVAs, paired t-tests, and effect size calculations over defined time intervals. Post-hoc power analyses suggested that a future study should employ a sample size of about 21 case group participants in order to detect a statistically significant change in pain intensity (Appendix A), whereas 12 to 13 participants are required for measures of pain interference (Appendices B-C). However, the results of this small pilot study were consistent with what might be expected based upon the conceptual focus of mindfulness meditation, and the effect sizes were of reasonable magnitude to draw some limited interpretations.

Challenges were met with recruiting and retention in this Veteran cohort due to limited transportation alternatives, physical mobility, and expendability of income, which made the frequent visits to the DC VAMC (to attend biweekly iRest sessions and complete study measures) to be especially

difficult. For many potential study candidates and eventual participants, public transportation was not available to the DC VAMC, and as a result these patients were dependent on others for transportation. Among those who were able and willing to participate, one Veteran dropped out of the study due to work schedule, another was limited by transportation and physical mobility, and the third had commented on issues related to his work schedule before losing contact with the researchers. Finally, one patient was excluded due to a serious fall that was mainly attributed to physical mobility issues. Since only 69% of participants completed the study and were factored in to the final analysis, attrition may have affected the results due to unanticipated differences between those who were excluded vs. included (i.e. motivation, expectation). Furthermore it is plausible that those who were improving in pain-related symptoms remained in the treatment group, whereas patients who were not getting better dropped out of the study.

Study design, in combination with the aforementioned recruitment and retention difficulties, precludes us from generalizing the current findings to the overall population of individuals with chronic pain. In larger clinical trials with fewer inclusion criteria, internal validity is often a more important concern, whereas in smaller pilot studies with more stringent criteria as in the present study, generalization of results and statistical power are more pervasive. Although the sample size in the present study was inadequate to draw definitive conclusions, we attempted to include only the most rigorously screened individuals, substantially reducing the pool of potential participants. This feasibility study focused on male Veterans, because a considerable increase in sample size and additional research sites would have been required to adequately control for gender-specific variability in pain perception and neuroendocrine measures. Therefore the findings cannot be easily generalized towards women and other demographic characteristics that were not within the scope of the current study, including civilians, Veterans receiving medical care outside the VHA system, and chronic pain patients without comorbidities such as TBI. In addition, those who volunteered for the study may not be representative of all Veterans, since many declined to participate for a variety of reasons. Eventual study participants may have been more motivated to proactively manage their health condition, which would have led to more favorable study outcomes.

The homogeneity of the present study group (male, middle-age, OEF/OIF Veteran, VA out-patient, deployment-related TBI, chronic pain $\geq$ 5 on the NRS) provides a reasonable degree of internal

validity. However, despite random assignment, group membership between cases and controls at baseline was clinically unbalanced, which was likely the result of the extremely small sample size. It is possible that regression to the mean could explain the study results. The significant B-E reductions in pain interference and depression for the case group, for example, may have been attributed to the tendency for extreme scores to move in the direction of more moderate scores as seen in the control group, rather than exposure to iRest practice itself. The 3 participants with the highest pain interference scores on the DVPRS at baseline were members of the case group (Figures 19-20), making it possible that those with the greatest potential to improve happened to be in the experimental group. Furthermore, it is possible that other treatments received by the case and control group participants may have contributed to the results rather than the practice of iRest. All participants were only permitted to take NSAIDS for pain relief during the study, however many were receiving care as outpatients from their primary care provider, psychologist, social worker, or audiologist at the DC VAMC, which could have confounded the results. Finally, the widely varying comorbidities of these patients (chronic pain, TBI, PTSD, depression, obesity) adds complexity to disentangling the effects of any particular health issue on the outcome measures of interest.

Another limitation is the study's reliance on self-report measures of pain and emotional functioning, which may be subject to demand characteristics. Participant awareness of simply being involved in a study could have prompted them to respond in ways they believe were consistent with the researchers' hypotheses. Case patients may have felt more important due to the increased attention received from the iRest sessions, which may have predisposed them to give more favorable responses or to perform better than the controls who were perhaps less aware of the study's intent. However, there are many instances when individual participants reported the opposite of what would have been expected if demand characteristics were influencing outcome measures, such as a worsening of symptoms in case patients or corresponding improvements in control members. Nonetheless, control group participants were informed they would be receiving "routine symptom management" and it was probably known that they were serving as a control condition to be compared to an active intervention. This limitation could have been addressed by employing a more active control group (chronic pain education, social support) that met for a comparable amount of time as the iRest group. However due to limited availability of

resources, space, and staff, it was decided that the best option for the control condition would be standard medical care. Also, it was not possible to control for the different medical treatments received by each patient as part of their "standard medical care," which may have influenced the changes in outcome measures seen at endpoint and follow-up. These potentially confounding effects cannot be separated out in a clinical study of this kind.

Finally, because it was not logistically possible for the study to be blinded, knowledge of group membership may have caused researchers to act differently towards those in the case vs. control groups, thereby influencing participant behavior. The primary researcher was aware of this concern and took precautions to interact with study participants so that members of both groups were treated equitably and professionally without bias.

Future Directions

Despite these shortcomings the findings from this pilot study are encouraging, and highlight the therapeutic potential of a novel approach for those living with chronic pain who have exhausted all other treatment possibilities. The aim of this study was to examine the effectiveness of a mindfulness-based intervention as an adjunct or an alternative to conventional medical care. Further research is warranted to confirm the effectiveness of iRest for managing chronic pain in combat Veterans. Larger clinical trials are needed to provide greater statistical power and more reliable estimates of effect size. In addition, employing longer follow-up periods (3-month, 6-month, 1-year) into the study design would provide further insight concerning long-term compliance with iRest practice and maintenance of symptom improvements. Finally, to minimize participant burden for chronic pain patients who are physically and mentally impaired by multiple comorbidities, only the most vital multi-dimensional measures of chronic pain should be employed in the study design, and face-to-face participation could be reduced to one 2-hour iRest session per week. Audio recordings were beneficial in immersing case group patients in the practice of iRest. The Veterans appreciated the convenience of listening to the audio practice on their own, but all preferred the "live" practice with the instructor. Although integrating iRest into a telehealth model may not be ideal, it may serve as the only viable alternative for patients who live in rural areas, have limited physical mobility, or otherwise have inadequate access to a medical or clinical provider to help manage

their chronic pain. Because the availability of pain care is limited by a number of barriers—regulatory, legal, institutional, financial, and geographical—steps must be taken to improve access and quality of care that is tailored to each individual's experience (IOM, 2011). However, few available treatment options have been found to be effective for the long-term management of chronic pain. Since chronic pain involves many complex biological and psychosocial facets, and patients must live with and manage pain daily, health care providers should increasingly promote self-management of pain by disseminating strategies and techniques to help patients prevent, cope with, and reduce pain (IOM, 2011). iRest represents a promising multi-faceted self-management approach that is well suited to not only foster self-efficacy and empowerment, but to ultimately enable those with chronic pain to acquire the cognitive, behavioral, and emotional techniques and skills necessary to establish a satisfactory quality of life.

APPENDIX A

POWER ANALYSIS USING CASE GROUP DATA FOR THE VAS
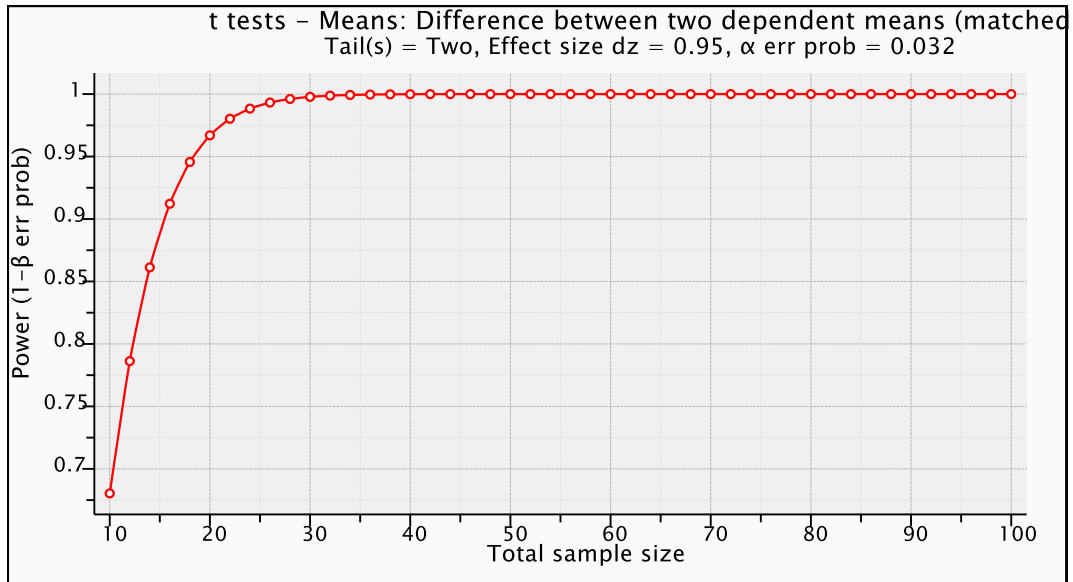
FROM BASELINE TO FOLLOW-UP
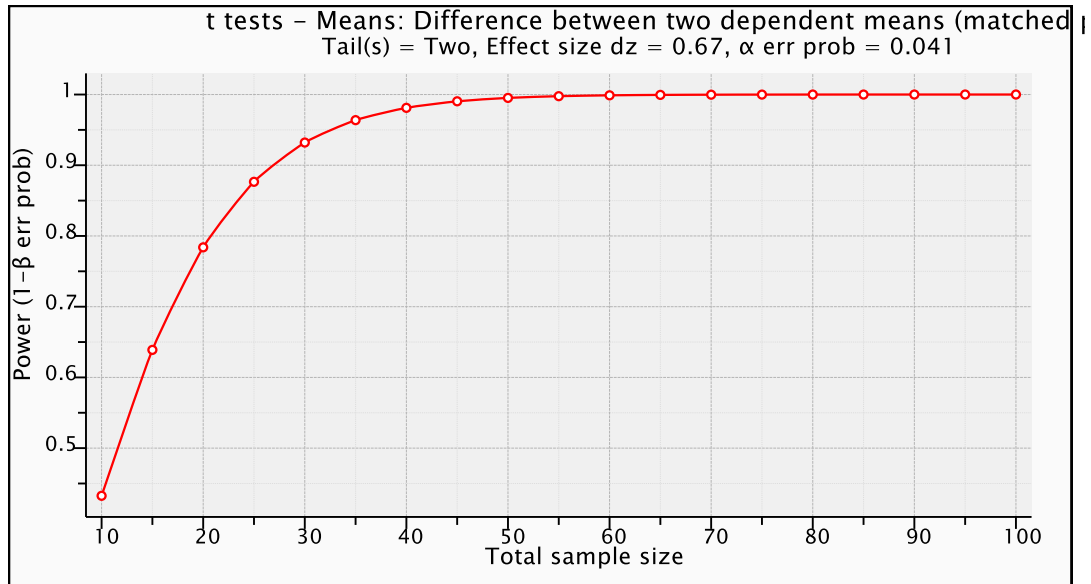
APPENDIX B

POWER ANALYSIS USING CASE GROUP DATA FOR DVPRS PAIN INTERFERENCE

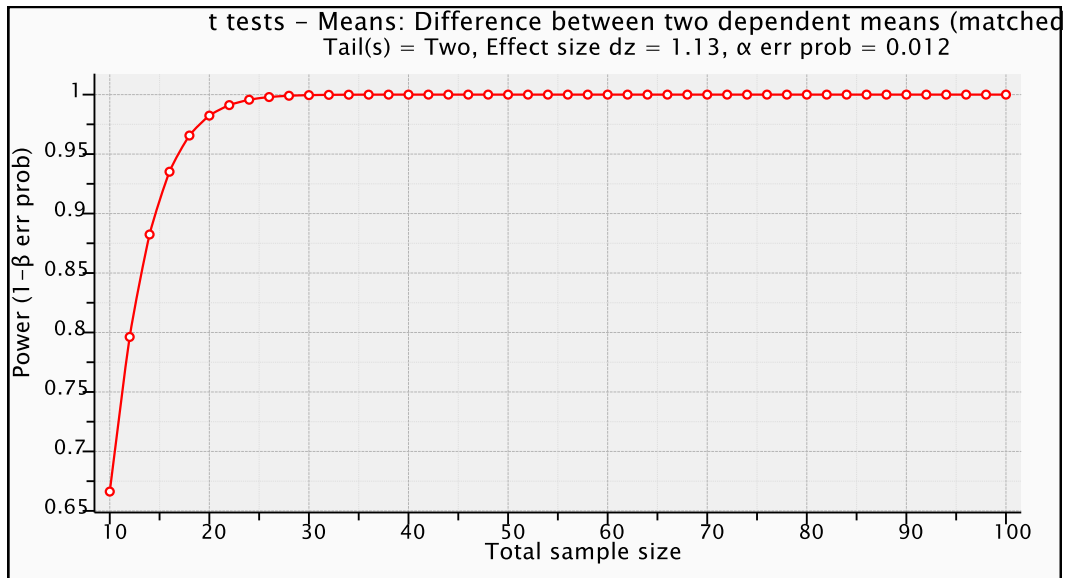## FROM BASELINE TO FOLLOW-UP

t tests – Means: Difference between two dependent means (matched)
Tail(s) = Two, Effect size dz = 0.95, α err prob = 0.032

APPENDIX C

POWER ANALYSIS USING CASE GROUP DATA FOR BPI PAIN INTERFERENCE

FROM BASELINE TO FOLLOW-UP

REFERENCES

Allen, N. B., Chambers, R., & Knight, W. (2006). Mindfulness-based psychotherapies: a review of conceptual foundations, empirical evidence and practical considerations. *Aust N Z J Psychiatry, 40*(4), 285-294.

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci, 19*(1), 484-494.

Ancoli-Israel, S. (2006). The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care, 12*(8 Suppl), S221-229.

Anderson, R. U., Orenberg, E. K., Chan, C. A., Morey, A., & Flores, V. (2008). Psychometric profiles and hypothalamic-pituitary-adrenal axis function in men with chronic prostatitis/chronic pelvic pain syndrome. *J Urol, 179*(3), 956-960.

Arnold, L. M., Hudson, J. I., Hess, E. V., Ware, A. E., Fritz, D. A., Auchenbach, M. B., et al. (2004). Family study of fibromyalgia. *Arthritis Rheum, 50*(3), 944-952.

Arnow, B. A., Hunkeler, E. M., Blasey, C. M., Lee, J., Constantino, M. J., Fireman, B., et al. (2006). Comorbid depression, chronic pain, and disability in primary care. *Psychosom Med, 68*(2), 262-268.

Ashburn, M. A., & Staats, P. S. (1999). Management of chronic pain. *Lancet, 353*(9167), 1865-1869.

Atkinson JH, Ancoli-Israel S, Slater MA, Garfin SR, Gillin JC. (1988). Subjective sleep disturbance in chronic back pain*. Clin J Pain*, 4, 225–32.

Atkinson, J. H., Jr., Kremer, E. F., Risch, S. C., Dana, R., & Janowsky, D. S. (1986). Neuroendocrine responses in psychiatric and pain patients with major depression. *Biol Psychiatry, 21*(7), 612-620.

Atkinson, J. H., Slater, M. A., Patterson, T. L., Grant, I., & Garfin, S. R. (1991). Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. *Pain, 45*(2), 111-121.

Austin, J. H. (1998). Zen and the brain: Toward an understanding of meditation and consciousness. Cambridge, MA: MIT Press.

Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical psychology: Science and practice*, *10*(2), 125-143.

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using self-report assessment methods to explore facets of mindfulness. Assessment, 13, 27-45.

BBN Corporation. (1996). *PROPHET StatGuide*. Retrieved from: http://www.angelfire.com/wv/bwhomedir/notes/nonpar.pdf

Bair, M. J., Matthias, M. S., Nyland, K. A., Huffman, M. A., Stubbs, D. L., Kroenke, K., et al. (2009). Barriers and facilitators to chronic pain self-management: a qualitative study of primary care patients with comorbid musculoskeletal pain and depression. *Pain Med, 10*(7), 1280-1290.

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Arch Intern Med, 163*(20), 2433-2445.

Baird, C. L., & Sands, L. (2004). A pilot study of the effectiveness of guided imagery with progressive muscle relaxation to reduce chronic pain and mobility difficulties of osteoarthritis. *Pain Manag Nurs, 5*(3), 97-104.

Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: a review. *Patient Educ Couns, 48*(2), 177-187.

Baron Short, E., Kose, S., Mu, Q., Borckardt, J., Newberg, A., George, M. S., et al. (2010). Regional brain activation during meditation shows time and practice effects: an exploratory FMRI study. *Evid Based Complement Alternat Med, 7*(1), 121-127.

Beck A.T., Steer RA and Brown GK (1996) "Manual for the Beck Depression Inventory-II". San Antonio, TX: Psychological Corporation

Becker, W. C., Fiellin, D. A., Gallagher, R. M., Barth, K. S., Ross, J. T., & Oslin, D. W. (2009). The association between chronic pain and prescription drug abuse in Veterans. *Pain Med, 10*(3), 531-536.

Bedard, M., Felteau, M., Mazmanian, D., Fedyk, K., Klein, R., Richardson, J., et al. (2003). Pilot evaluation of a mindfulness-based intervention to improve quality of life among individuals who sustained traumatic brain injuries. *Disabil Rehabil, 25*(13), 722-731.

Beehler, G. P., Rodrigues, A. E., Mercurio-Riley, D., & Dunn, A. S. (2013). Primary Care Utilization among Veterans with Chronic Musculoskeletal Pain: A Retrospective Chart Review. *Pain Med*.

Bendtsen, P., Hensing, G., Ebeling, C., & Schedin, A. (1999). What are the qualities of dilemmas experienced when prescribing opioids in general practice? *Pain, 82*(1), 89-96.

Berg, A., Oster, K., Janig, H., Likar, R., Pipam, W., Scholz, A., et al. (2009). Objective measurement of chronic pain by a complex concentration test. *Review of Psychology, 16*(1), 37-46.

Bergman, S. (2007). Management of musculoskeletal pain. *Best Pract Res Clin Rheumatol, 21*(1), 153-166.

Berkley, K. J. (1997). Sex differences in pain. *Behav Brain Sci, 20*(3), 371-380; discussion 435-513.

Bhogaonker, Priya. (2012) *Impact of Brief Meditation Training on Stress, Distress, and Quality of Life for Homeless Adults* (Doctoral dissertation). California Institute of Integral Studies, San Francisco, CA. Retrieved from: http://www.irest.us/sites/default/files/COTSResearchResults_Priya_Dissertation0913.pdf

Birdsall, B., Pritchard, M., Elison-Bowers, P., & Spann, J. (2011). Does Integrative Restoration (iRest) Meditation Decrease Perceived Stress Levels and Negative Moods in School Counselors?. *Vistas*, *11*(3), 1-8. Retrieved from http://www.counselingoutfitters.com/vistas/vistas11/Article_84.pdf

Borchardt, A. R., Patterson, S. M., & Seng, E. K. (2012). The effect of meditation on cortisol: A comparison of meditation techniques to a control group. Retrieved from https://www.google.com/url?q=http://www.irest.us/sites/default/files/Meditation%2520on%2520Co rtisol%252012.pdf&sa=U&ei=kUhIUpmUCYzS9gTHzYGoBA&ved=0CAcQFjAA&client=internal-uds-cse&usg=AFQjCNHRWwaSZyc1s6weshQbAvgtj6pwwA

Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Hals, E. K., et al. (2008). Assessment of pain. *Br J Anaesth, 101*(1), 17-24.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain, 10*(4), 287-333.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry, 156*(11), 1787-1795.

Buckenmaier, C. C., 3rd, Galloway, K. T., Polomano, R. C., McDuffie, M., Kwon, N., & Gallagher, R. M. (2013). Preliminary validation of the Defense and Veterans Pain Rating Scale (DVPRS) in a military population. *Pain Med, 14*(1), 110-123.

Cahn, B. R., & Polich, J. (2006). Meditation states and traits: EEG, ERP, and neuroimaging studies. *Psychol Bull, 132*(2), 180-211.

Calogero, A. E., Bernardini, R., Gold, P. W., & Chrousos, G. P. (1988). Regulation of rat hypothalamic corticotropin-releasing hormone secretion in vitro: potential clinical implications. *Adv Exp Med Biol, 245*, 167-181.

Carmody, J., & Baer, R. A. (2008). Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. *J Behav Med, 31*(1), 23-33.

Casey, K. L., Svensson, P., Morrow, T. J., Raz, J., Jone, C., & Minoshima, S. (2000). Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol, 84*(1), 525-533.

Centre for Evaluation & Monitoring. (2013). *Effect Size Calculator*. Durham University. Retrieved from http://www.cem.org/evidence-based-education/effect-size-calculator.

Chapman, J. B., Lehman, C. L., Elliott, J., & Clark, J. D. (2006). Sleep quality and the role of sleep medications for veterans with chronic pain. *Pain Med, 7*(2), 105-114.

Cherry, D. K., Burt, C. W., & Woodwell, D. A. (2003). National Ambulatory Medical Care Survey: 2001 summary. *Adv Data*(337), 1-44.

Cimmino, M. A., Ferrone, C., & Cutolo, M. (2011). Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol, 25*(2), 173-183.

Clark, J. D. (2002). Chronic pain prevalence and analgesic prescribing in a general medical population. *J Pain Symptom Manage, 23*(2), 131-137.

Clark, L. G., & Upshur, C. C. (2007). Family medicine physicians' views of how to improve chronic pain management. *J Am Board Fam Med, 20*(5), 479-482.

Clark, M. E. (2004). Post-deployment pain: a need for rapid detection and intervention. *Pain Med, 5*(4), 333-334.

Cleeland CS, Ryan KM. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 23(2), 129-138.

Cleeland, C. S., Gonin, R., Hatfield, A. K., Edmonson, J. H., Blum, R. H., Stewart, J. A., et al. (1994). Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med, 330*(9), 592-596.

The Cochrane Collaboration. (2002). *Intention to Treat Issues*. Retrieved from http://www.cochrane net.org/openlearning/HTML/mod14-4.htm

Cohen J. (1977). *Statistical power analysis for the behavioral sciences*. New York: Academic Press.

Cohen, M.J.M., Menefee, L.A., Doghramji, K., Andersen W.R., & Frank E.D. (2000). Sleep in chronic pain problems and treatments. *Int Rev Psych*, 12, 115–27.

Conners, C. K. Multi Health Systems (MHS). *Conners' Continuous Performance Test II: Technical guide for software manual*. New York: Multi-Health Systems; 2004.

Cuellar, N. G. (2008). Mindfulness meditation for veterans---implications for occupational health providers. *AAOHN J, 56*(8), 357-363.

Curatolo, M., & Bogduk, N. (2001). Pharmacologic pain treatment of musculoskeletal disorders: current perspectives and future prospects. *Clin J Pain, 17*(1), 25-32.

Dale Berger, *Introduction to One-Way Analysis of Variance*. Claremont Graduate University. Retrieved from wise.cgu.edu/downloads/ANOVA.doc

De Jongh, R. F., Vissers, K. C., Meert, T. F., Booij, L. H., De Deyne, C. S., & Heylen, R. J. (2003). The role of interleukin-6 in nociception and pain. *Anesth Analg, 96*(4), 1096-1103, table of contents.

de Winter, J. C. F. (2013). Using the Student's t-test with extremely small sample sizes. *Practical Assessment, Research & Evaluation*, *18*(10), 2.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci U S A, 102*(51), 18626-18631.

Department of Veterans Affairs. (2013). *Using the PTSD Checklist (PCL)*. National Center for PTSD. Retrieved from http://www.ptsd.va.gov/professional/pages/assessments/assessment-pdf/PCL-handout.pdf

DeRijk, R., Michelson, D., Karp, B., Petrides, J., Galliven, E., Deuster, P., et al. (1997). Exercise and circadian rhythm-induced variations in plasma cortisol differentially regulate interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha (TNF alpha) production in humans: high sensitivity of TNF alpha and resistance of IL-6. *J Clin Endocrinol Metab, 82*(7), 2182-2191.

Dersh, J., Gatchel, R. J., Mayer, T., Polatin, P., & Temple, O. R. (2006). Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. *Spine (Phila Pa 1976), 31*(10), 1156-1162.

Dick, B. D., & Rashiq, S. (2007). Disruption of attention and working memory traces in individuals with chronic pain. *Anesth Analg, 104*(5), 1223-1229, tables of contents.

Dick, B. D., Verrier, M. J., Harker, K. T., & Rashiq, S. (2008). Disruption of cognitive function in fibromyalgia syndrome. *Pain, 139*(3), 610-616.

Dobscha, S. K., Corson, K., Flores, J. A., Tansill, E. C., & Gerrity, M. S. (2008). Veterans affairs primary care clinicians' attitudes toward chronic pain and correlates of opioid prescribing rates. *Pain Med, 9*(5), 564-571.

Drewes A.M., & Arendt-Nielsen L. (2001). Pain and sleep in medical diseases: interactions and treatment possibilities a review. *Sleep Research Online*, 4, 67–76.

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., et al. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain, 9*(2), 105-121.

Dworkin, S. F., Von Korff, M., & LeResche, L. (1990). Multiple pains and psychiatric disturbance. An epidemiologic investigation. *Arch Gen Psychiatry, 47*(3), 239-244.

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull, 125*(3), 356-366.

Eccleston, C., & Crombez, G. (2007). Worry and chronic pain: a misdirected problem solving model. *Pain, 132*(3), 233-236.

Elomaa, M. M., de, C. W. A. C., & Kalso, E. A. (2009). Attention management as a treatment for chronic pain. *Eur J Pain, 13*(10), 1062-1067.

Engel, C.Jr., Choate,C. G., Cockfield, D., Armstrong, D. W., Jonas, W., Joan, A. G., & Miller, R. Yoga Nidra as an adjunctive therapy for post- traumatic stress disorder: A feasibility study. Retrieved from http://www.irest.us/sites/default/files/WRAMH_PTSD_YN_Results_0.pdf

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science, 196*(4286), 129-136.

Epel, E., Daubenmier, J., Moskowitz, J. T., Folkman, S., & Blackburn, E. (2009). Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. Annals of the New York Academy of Sciences, 1172, 34–53.

Eriksen, J., Sjogren, P., Bruera, E., Ekholm, O., & Rasmussen, N. K. (2006). Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain, 125*(1-2), 172-179.

Faul, M., Xu, L., Wald, M., & Coronado, V. (2010). *Traumatic Brain Injury in the United States: Emergency*

Fillingim, R. B. (2000). Sex, gender, and pain: women and men really are different. *Curr Rev Pain, 4*(1), 24-30.

Fishbain, D. A., Cole, B., Cutler, R. B., Lewis, J., Rosomoff, H. L., & Fosomoff, R. S. (2003). Is pain fatiguing? A structured evidence-based review. *Pain Med, 4*(1), 51-62.

Fishbain, D. A., Cutler, R., Rosomoff, H. L., & Rosomoff, R. S. (1997). Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain, 13*(2), 116-137.

Flanagan, S. R., Cantor, J. B., & Ashman, T. A. (2008). Traumatic brain injury: future assessment tools and treatment prospects. *Neuropsychiatr Dis Treat, 4*(5), 877-892.

Freburger, J. K., Holmes, G. M., Agans, R. P., Jackman, A. M., Darter, J. D., Wallace, A. S., et al. (2009). The rising prevalence of chronic low back pain. *Arch Intern Med, 169*(3), 251-258.

Gallagher, R. M. (2009). Biopsychosocial pain research in America: the Veterans Health System leads the way. *Pain Med, 10*(7), 1165-1166.

Gaskin, D. J., & Richard, P. (2012). The economic costs of pain in the United States. *J Pain, 13*(8), 715-724.

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull, 133*(4), 581-624.

Gironda, R. J., Clark, M. E., Massengale, J. P., & Walker, R. L. (2006). Pain among veterans of Operations Enduring Freedom and Iraqi Freedom. *Pain Med, 7*(4), 339-343.

Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988a). Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (Part 1 of 2). *N Engl J Med, 319*(6), 348-353.

Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988b). Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (Part 2 of 2). *N Engl J Med, 319*(7), 413-420.

Gold, P. W., Kling, M. A., Whitfield, H. J., Rabin, D., Margioris, A., Kalogeras, K., et al. (1988). The clinical implications of corticotropin-releasing hormone. *Adv Exp Med Biol, 245*, 507-519.

Gold, P. W., & Chrousos, G. P. (1999). The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc Assoc Am Physicians, 111*(1), 22-34.

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry, 7*(3), 254-275.

Gold, P. W., Wong, M. L., Chrousos, G. P., & Licinio, J. (1996). Stress system abnormalities in melancholic and atypical depression: molecular, pathophysiological, and therapeutic implications. *Mol Psychiatry, 1*(4), 257-264.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., et al. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127*(Pt 4), 835-843.

Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in Zen meditators: a cross-sectional study. *Psychosom Med, 71*(1), 106-114.

Grant, J. A., Courtemanche, J., Duerden, E. G., Duncan, G. H., & Rainville, P. (2010). Cortical thickness and pain sensitivity in zen meditators. *Emotion, 10*(1), 43-53.

Green, C. R., Wheeler, J. R., Marchant, B., LaPorte, F., & Guerrero, E. (2001). Analysis of the physician variable in pain management. *Pain Med, 2*(4), 317-327.

Green, S. B., & Salkind, N. J. (2003). *Using SPSS: Analyzing and understanding data, 3rd ed.* Upper Saddle River, NJ: Prentice Hall

Greenberger, P. (2001). Women, Men, and Pain. *Journal of Women's Health & Gender-Based Medicine, 10*(4), 309-310.

Gross JJ. (1998). The emerging field of emotion regulation: An integrative review. *Rev Gen Psychol*, 2(3), 271–99.

Hardt, J., Jacobsen, C., Goldberg, J., Nickel, R., & Buchwald, D. (2008). Prevalence of chronic pain in a representative sample in the United States. *Pain Med, 9*(7), 803-812.

Haskell, S. G., Brandt, C. A., Krebs, E. E., Skanderson, M., Kerns, R. D., & Goulet, J. L. (2009). Pain among Veterans of Operations Enduring Freedom and Iraqi Freedom: do women and men differ? *Pain Med, 10*(7), 1167-1173.

Hedges, Larry V. (1981). Distribution theory for Glass's estimator of effect size and related estimators, *Journal of Educational Statistics 6 (2):* 107–128.

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., et al. (2003). Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. *Neuroimage, 19*(3), 587-600.

Hildreth, C. J. (2009). Combat injuries in Iraq and Afghanistan help rewrite the book on war surgery. *JAMA, 301*(18), 1866-1867.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med, 358*(5), 453-463.

Holzel, B. K., Ott, U., Gard, T., Hempel, H., Weygandt, M., Morgen, K., et al. (2008). Investigation of mindfulness meditation practitioners with voxel-based morphometry. *Soc Cogn Affect Neurosci, 3*(1), 55-61.

Hudson, J. I., Arnold, L. M., Keck, P. E., Jr., Auchenbach, M. B., & Pope, H. G., Jr. (2004). Family study of fibromyalgia and affective spectrum disorder. *Biol Psychiatry, 56*(11), 884-891.

Institute of Medicine (IOM). 2011. *Care and Education Committee on Advancing Pain Research, Relieving pain in America: a blueprint for transforming prevention, care, education, and research*. Washington DC: National Academies Press.

Institute of Medicine Committee on Identifying Priority Areas for Quality Improvement (2003). *Priority areas for national action: Transforming health care*. Washington, DC: National Academies Press.

Jha, A. P., Krompinger, J., & Baime, M. J. (2007). Mindfulness meditation modifies subsystems of attention. *Cognitive Affective Behavioral Neuroscience*, 7(2), 109–119.

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain, 11*(11), 1230-1239.

Joranson, D. E., Ryan, K. M., Gilson, A. M., & Dahl, J. L. (2000). Trends in medical use and abuse of opioid analgesics. *JAMA, 283*(13), 1710-1714.

Kabat-Zinn, J. (1982). An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry, 4*(1), 33-47.

Keefe, F. J., Somers, T. J., & Martire, L. M. (2008). Psychologic interventions and lifestyle modifications for arthritis pain management. *Rheum Dis Clin North Am, 34*(2), 351-368.

Kerns, R. D., & Dobscha, S. K. (2009). Pain among veterans returning from deployment in Iraq and Afghanistan: update on the Veterans Health Administration Pain Research Program. *Pain Med, 10*(7), 1161-1164.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annu Rev Psychol, 53*, 83-107.

Kingston, J., Chadwick, P., Meron, D., & Skinner, T. C. (2007). A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity. *J Psychosom Res, 62*(3), 297-300.

Kiran, U., Behari, M., Venugopal P., Vivekananda S., & Pandey R.M. (2005). The effect of Autogenic relaxation on chronic tension headache and in modulating cortisol response. *Indian j Anaesthesia*, 49(6):474-8.

Koch, H. (1986). *The management of chronic pain in office-based ambulatory care: National Ambulatory Medical Care Survey*, National Center for Health Statistics Report, DHHS Pub. No. 86-1250.

Kroenke, K. (2003). Patients presenting with somatic complaints: epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res, 12*(1), 34-43.

Kroenke, K., Bair, M. J., Damush, T. M., Wu, J., Hoke, S., Sutherland, J., et al. (2009). Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA, 301*(20), 2099-2110.

Kroenke, K., Krebs, E., Wu, J., Bair, M. J., Damush, T., Chumbler, N., et al. (2013). Stepped Care to Optimize Pain care Effectiveness (SCOPE) trial study design and sample characteristics. *Contemp Clin Trials, 34*(2), 270-281.

Legrain, V., Damme, S. V., Eccleston, C., Davis, K. D., Seminowicz, D. A., & Crombez, G. (2009). A neurocognitive model of attention to pain: behavioral and neuroimaging evidence. *Pain, 144*(3), 230-232.

Levine, J. D., & Reichling, D. B. (1999). Peripheral mechanisms of inflammatory pain. In P. D. Wall & R. Melzack (Eds.), *Textbook of pain* (4th ed., pp. 59–84). New York: Churchill Livingstone.

Lew, H. L., Otis, J. D., Tun, C., Kerns, R. D., Clark, M. E., & Cifu, D. X. (2009). Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. *J Rehabil Res Dev, 46*(6), 697-702.

Lin, E. H., Katon, W., Von Korff, M., Tang, L., Williams, J. W., Jr., Kroenke, K., et al. (2003). Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA, 290*(18), 2428-2429.

Lutz, A., Slagter, H. A., Rawlings, N. B., Francis, A. D., Greischar, L. L., & Davidson, R. J. (2009). Mental training enhances attentional stability: neural and behavioral evidence. *J Neurosci, 29*(42), 13418-13427.

Magni, G., Marchetti, M., Moreschi, C., Merskey, H., & Luchini, S. R. (1993). Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination. I. Epidemiologic follow-up study. *Pain, 53*(2), 163-168.

Magni, G., Moreschi, C., Rigatti-Luchini, S., & Merskey, H. (1994). Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain, 56*(3), 289-297.

Manocchia, M., Keller, S., & Ware, J. E. (2001). Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. *Qual Life Res, 10*(4), 331-345.

Matthias, M. S., Bair, M. J., Nyland, K. A., Huffman, M. A., Stubbs, D. L., Damush, T. M., et al. (2010a). Self-management support and communication from nurse care managers compared with primary care physicians: a focus group study of patients with chronic musculoskeletal pain. *Pain Manag Nurs, 11*(1), 26-34.

Matthias, M. S., Parpart, A. L., Nyland, K. A., Huffman, M. A., Stubbs, D. L., Sargent, C., et al. (2010b). The patient-provider relationship in chronic pain care: providers' perspectives. *Pain Med, 11*(11), 1688-1697.

Matthias, M. S., Miech, E. J., Myers, L. J., Sargent, C., & Bair, M. J. (2012a). An expanded view of self-management: patients' perceptions of education and support in an intervention for chronic musculoskeletal pain. *Pain Med, 13*(8), 1018-1028.

Matthias, M. S., Miech, E. J., Myers, L. J., Sargent, C., & Bair, M. J. (2012b). "There's more to this pain than just pain": how patients' understanding of pain evolved during a randomized controlled trial for chronic pain. *J Pain, 13*(6), 571-578.

McBeth, J., & Jones, K. (2007). Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol, 21*(3), 403-425.

McBeth, J., Chiu, Y. H., Silman, A. J., Ray, D., Morriss, R., Dickens, C., et al. (2005). Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Res Ther, 7*(5), R992-R1000.

McBeth, J., Silman, A. J., Gupta, A., Chiu, Y. H., Ray, D., Morriss, R., et al. (2007). Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. *Arthritis Rheum, 56*(1), 360-371.

McCracken, L. M., Gauntlett-Gilbert, J., & Vowles, K. E. (2007). The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain, 131*(1-2), 63-69.

McCracken, L.M., & Thompson, M. (2009). Components of mindfulness in patients with chronic pain. *J Psychopathol Behav Asses*, 31(2), 75–82.

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain, 111*(1-2), 77-83.

Mead, N., & Bower, P. (2000). Patient-centredness: a conceptual framework and review of the empirical literature. *Soc Sci Med, 51*(7), 1087-1110.

Melzack, R. (1999). Pain--an overview. *Acta Anaesthesiol Scand, 43*(9), 880-884.

Melzack, R. (2005). Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. *Pain Pract, 5*(2), 85-94.

Melzack, R., & Wall, P. D. (1996). *The Challenge of Pain*. New York: Penguin.

Merskey H., & Bogduk N. (1994). *International Association for the Study of Pain Task Force on Taxonomy*. Seattle, WA: IASP Press, 209–14

Merton, L., Wardrop, R., Hadlow, N. The effect of increased body mass index on serum cortisol levels. *Western Diagnostic Pathology*. Retrieved from http://oldsite.aacb.asn.au/files/File/Posters%20ASC%202011/P59%20L%20MERTON.PDF

Meyer, T., Cooper, J., & Raspe, H. (2007). Disabling low back pain and depressive symptoms in the community-dwelling elderly: a prospective study. *Spine (Phila Pa 1976), 32*(21), 2380-2386.

Miller, L. R., & Cano, A. (2009). Comorbid chronic pain and depression: who is at risk? *J Pain, 10*(6), 619-627.

Mitka, M. (2003). Experts debate widening use of opioid drugs for chronic nonmalignant pain. *JAMA, 289*(18), 2347-2348.

Moldin, S. O., Scheftner, W. A., Rice, J. P., Nelson, E., Knesevich, M. A., & Akiskal, H. (1993). Association between major depressive disorder and physical illness. *Psychol Med, 23*(3), 755-761.

Moore, A., & Malinowski, P. (2009). Meditation, mindfulness and cognitive flexibility. *Conscious Cogn, 18*(1), 176-186.

Morin, C. M., Gibson, D., & Wade, J. (1998). Self-reported sleep and mood disturbance in chronic pain patients. *Clin J Pain, 14*(4), 311-314.

Nampiaparampil, D. E. (2008). Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA, 300*(6), 711-719.

National Center for Health Statistics. (2006). *Department Visits, Hospitalizations and Deaths 2002–2006*. Centers for Disease Control: Atlanta, GA.

National Research Council (NRC) & Institute of Medicine (IOM). 2000. *Musculoskeletal disorder and the workplace: low back and upper extremities*. National Academy Press.

National Research Council (NRC). (2010). The Prevention and Treatment of Missing Data in Clinical Trials. The National Academies Press. Retrieved from http://www.nap.edu/catalog.php?record_id=12955

Nedeljkovic, S. S., Wasan, A., & Jamison, R. N. (2002). Assessment of efficacy of long-term opioid therapy in pain patients with substance abuse potential. *Clin J Pain, 18*(4 Suppl), S39-51.

Nicholas, M. K. (2008). Pain management in musculoskeletal conditions. *Best Pract Res Clin Rheumatol, 22*(3), 451-470.

Nicholas, M. K., Asghari, A., Blyth, F. M., Wood, B. M., Murray, R., McCabe, R., et al. (2013). Self-management intervention for chronic pain in older adults: A randomised controlled trial. *Pain, 154*(6), 824-835.

Ofek, H., & Defrin, R. (2007). The characteristics of chronic central pain after traumatic brain injury. *Pain, 131*(3), 330-340.

Ohayon, M. M. (2005). Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res, 39*(2), 151-159.

Ohayon, M. M., & Schatzberg, A. F. (2003). Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry, 60*(1), 39-47.

Okie, S. (2005). Traumatic brain injury in the war zone. *N Engl J Med, 352*(20), 2043-2047.

Otis, J. D., Keane, T. M., Kerns, R. D., Monson, C., & Scioli, E. (2009). The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic stress disorder. *Pain Med, 10*(7), 1300-1311.

Petrovic, P., & Ingvar, M. (2002). Imaging cognitive modulation of pain processing. *Pain, 95*(1-2), 1-5.

Plews-Ogan, M., Owens, J. E., Goodman, M., Wolfe, P., & Schorling, J. (2005). A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain. *J Gen Intern Med, 20*(12), 1136-1138.

Portenoy, R., Ugarte, C., Fuller, I., & Haas, G. (2004). Population-Based Survey of Pain in the United States: Differences Among White, African American, and Hispanic Subjects. *The Journal of Pain, 5*(6), 317-328.

Potter, M., Schafer, S., Gonzalez-Mendez, E., Gjeltema, K., Lopez, A., Wu, J., et al. (2001). Opioids for chronic nonmalignant pain. Attitudes and practices of primary care physicians in the UCSF/Stanford Collaborative Research Network. University of California, San Francisco. *J Fam Pract, 50*(2), 145-151.

President's Commission on Care for America's Returning Wounded Warriors. 2007. Rehabilitation. In *Serve, support, simplify: Subcommittee reports and survey findings.* Retrieved from http://www.veteransforamerica.org/wp-content/uploads/2008/12/presidents-commission-on-care-for-americas-returning-wounded-warriors-report-july-2007.pdf

Pritchard, M., Elison-Bowers, P., & Birdsall, B. (2009). Impact of integrative restoration (iRest) meditation on perceived stress levels in multiple sclerosis and cancer outpatients. *Stress and Health, 26(3),* 233–237.

Raja, S. N., Meyer, R. A., Ringkamp, M., & Campbell, J. A. (1999). Peripheral neural mechanisms of nociception. In P. D. Wall & R. Melzack (Eds.), *Textbook of pain* (4th ed., pp. 11–58). New York: Churchill Livingstone.

Rees, B. (2011). Overview of outcome data of potential meditation training for soldier resilience. *Mil Med, 176*(11), 1232-1242.

Reiner, K., Tibi, L., & Lipsitz, J. D. (2013). Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Med, 14*(2), 230-242.

Reinhard, Matthew, et al. (2012). Acupuncture and Meditation for Military Veterans: Patient Satisfaction and Self-Reported Symptom Reduction. *War Related Illness and Injury Study Center, Washington, DC Veterans Affairs Medical Center*.

Riley, J. L., 3rd, Robinson, M. E., Wise, E. A., Myers, C. D., & Fillingim, R. B. (1998). Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain, 74*(2-3), 181-187.

Romesser, J., Booth, J., Benge, J., Pastorek, N., & Helmer, D. (2012). Mild traumatic brain injury and pain in Operation Iraqi Freedom/Operation Enduring Freedom veterans. *J Rehabil Res Dev, 49*(7), 1127-1136.

Rosenzweig, S., Greeson, J. M., Reibel, D. K., Green, J. S., Jasser, S. A., & Beasley, D. (2010). Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice. *J Psychosom Res, 68*(1), 29-36.

Rudy, T. E., Kerns, R. D., & Turk, D. C. (1988). Chronic pain and depression: toward a cognitive-behavioral mediation model. *Pain, 35*(2), 129-140.

Sarlani, E., Grace, E. G., Reynolds, M. A., & Greenspan, J. D. (2004). Sex differences in temporal summation of pain and aftersensations following repetitive noxious mechanical stimulation. *Pain, 109*(1-2), 115-123.

Sartorio, A., Agosti, F., Patrizi, A., Gattico, A., Tringali, G., Giunta, M., Muller, & E.E., Rigamonti, A.E. (2013). GH and cortisol responses following an acute session of respiratory muscle endurance training in severely obese patients. *Hormone and Metabolic Research*, 45(3): 239-44.

Schmidt-Wilcke, T., Leinisch, E., Ganssbauer, S., Draganski, B., Bogdahn, U., Altmeppen, J., et al. (2006). Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain, 125*(1-2), 89-97.

Seal, K. H., Metzler, T. J., Gima, K. S., Bertenthal, D., Maguen, S., & Marmar, C. R. (2009). Trends and risk factors for mental health diagnoses among Iraq and Afghanistan veterans using Department of Veterans Affairs health care, 2002-2008. *Am J Public Health, 99*(9), 1651-1658.

Sherbourne, C. D., Asch, S. M., Shugarman, L. R., Goebel, J. R., Lanto, A. B., Rubenstein, L. V., et al. (2009). Early identification of co-occurring pain, depression and anxiety. *J Gen Intern Med, 24*(5), 620-625.

Slagter, H. A., Lutz, A., Greischar, L. L., Francis, A. D., Nieuwenhuis, S., Davis, J. M., et al. (2007). Mental training affects distribution of limited brain resources. *PLoS Biol, 5*(6), e138.

Smallwood, J., Fitzgerald, A., Miles, L. K., & Phillips, L. H. (2009). Shifting moods, wandering minds: negative moods lead the mind to wander. Emotion, 9(2), 271–276.

Smallwood, J., McSpadden, M., & Schooler, J. W. (2007). The lights are on but no one's home: Meta-awareness and the decoupling of attention when the mind wanders. Psychonomic Bulletin and Review, 14(3), 527–533.

Solberg, N.L., Roach, A.R., & Segerstrom, S.C. Executive functions, self-regulation, and chronic pain: A review. *Ann Behav Med*, 37(2),173–83.

Spelman, J. F., Hunt, S. C., Seal, K. H., & Burgo-Black, A. L. (2012). Post deployment care for returning combat veterans. *J Gen Intern Med, 27*(9), 1200-1209.

Stankovic, L. (2011). Transforming trauma: a qualitative feasibility study of integrative restoration (iRest) yoga Nidra on combat-related post-traumatic stress disorder. *Int J Yoga Therap*(21), 23-37.

Stanley, E. A., & Jha, A. P. (2009). Mind fitness: Improving operational effectiveness and building warrior resilience. *Joint Force Quarterly: JFQ*, (55), 144.

Stevenson, C. (2009). Evolving mechanisms and patterns of blast injury and the challenges for military first responders. *Journal of Military and Veterans' Health, 17*(4), 17-21.

Stewart M., Brown J.B., & Weston W.W., et al. (1995). *Patient- Centered Medicine: Transforming the Clinical Method*. Thousand Oaks, CA: Sage.

Stewart, W., Ricci, J., Chee, E., Morganstein, D., & Lipton, R. (2004). Lost productive time and cost due to common pain conditions in the US workforce. *JAMA, 290*(18), 2443-2454.

Streiner, D. L. (2013). The Case of the Missing Data: Methods of Dealing with Dropouts and Other Research Vagaries. *A Guide to the Statistically Perplexed: A Compilation of Readings from the Canadian Journal of Psychiatry*, *47*, 83.

Tang, Y. Y., & Posner, M. I. (2009). Attention training and attention state training. *Trends Cogn Sci, 13*(5), 222-227.

Tang, Y. Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., et al. (2007). Short-term meditation training improves attention and self-regulation. *Proc Natl Acad Sci U S A, 104*(43), 17152-17156.

Tanielian, T., & Jaycox, L. H. (2008). *Invisible wounds of war: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery*. CA: RAND.

Teasdale, J. D. (1999). Metacognition, mindfulness, and the modification of mood disorders. *Clinical Psychology and Psycho- therapy, 6,* 146–155.

Teasdale, J. D., Segal, Z., & Williams, J. M. (1995). How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? *Behav Res Ther, 33*(1), 25-39.

Tennant, F., & Hermann, L. (2001). Serum Cortisol Concentrations and Adrenal Reserve May Be Altered by Severe Chronic Pain. *Pain Medicine, 2*(3), 252-252.

Tennant, F., & Hermann, L. (2002). Normalization of serum cortisol concentration with opioid treatment of severe chronic pain. *Pain Med, 3*(2), 132-134.

Thomas, G. A., Kraemer, W. J., Comstock, B. A., Dunn-Lewis, C., Volek, J. S., Denegar, C. R., & Maresh, C. M. (2012). Effects of resistance exercise and obesity level on ghrelin and cortisol in men. *Metabolism*, *61*(6), 860-868.

Todd, K. H., Samaroo, N., & Hoffman, J. R. (1993). Ethnicity as a risk factor for inadequate emergency department analgesia. *JAMA, 269*(12), 1537-1539.

Travison, T. G., O'Donnell, A. B., Araujo, A. B., Matsumoto, A. M., & McKinlay, J. B. (2007). Cortisol levels and measures of body composition in middle-aged and older men. *Clinical endocrinology*, *67*(1), 71-77.

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., ... & Watanabe, M. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The journal of pain*, *9*(10), 883-891.

Turk, D. C. (2002). Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. *Clin J Pain, 18*(6), 355-365.

Turk, D. C., & Okifuji, A. (2002). Psychological factors in chronic pain: evolution and revolution. *J Consult Clin Psychol, 70*(3), 678-690.

Turk, D. C., Brody, M. C., & Okifuji, E. A. (1994). Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain, 59*(2), 201-208.

Tuzun, E. H. (2007). Quality of life in chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol, 21*(3), 567-579.

University of Iowa. (2006). Russ Length's Power and Sample Size: Retrieved from http://www.cs.uiowa.edu/~rlenth/Power/.

Upshur, C. C., Luckmann, R. S., & Savageau, J. A. (2006). Primary care provider concerns about management of chronic pain in community clinic populations. *J Gen Intern Med, 21*(6), 652-655.

Valentine, E. R., & Sweet, P. L. (1999). Meditation and attention: A comparison of the effects of concentrative and mindfulness meditation on sustained attention. *Mental Health, Religion & Culture*, *2*(1), 59-70.

Van Cauter, E., Leproult, R., & Kupfer, D. J. (1996). Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab, 81*(7), 2468-2473.

Van Uum, S. H., Sauve, B., Fraser, L. A., Morley-Forster, P., Paul, T. L., & Koren, G. (2008). Elevated content of cortisol in hair of patients with severe chronic pain: a novel biomarker for stress. *Stress, 11*(6), 483-488.

Veehof, M. M., Oskam, M. J., Schreurs, K. M., & Bohlmeijer, E. T. (2011). Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain, 152*(3), 533-542.

Veterans Health Administration (VHA) Memorandum: *Pain as the Fifth Vital Sign*. March 1, 1999.

Veterans Health Administration (VHA). (2011). *Analysis of VA Health Care Utilization among Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) Veterans*. Office of Public Health and Environmental Hazards Quarterly Report. Department of Veterans Affairs, November 2011.

Von Korff, M., Dworkin, S. F., Le Resche, L., & Kruger, A. (1988). An epidemiologic comparison of pain complaints. *Pain, 32*(2), 173-183.

Von Korff, M., Kolodny, A., Deyo, R. A., & Chou, R. (2011). Long-term opioid therapy reconsidered. *Ann Intern Med, 155*(5), 325-328.

Von Korff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the severity of chronic pain. *Pain, 50*(2), 133-149.

Wagner, E. H., Austin, B. T., & Von Korff, M. (1996). Organizing care for patients with chronic illness. *Milbank Q, 74*(4), 511-544.

Wallace, A. (2006). The attention revolution: Unlocking the power of the focused mind. Boston, MA: Wisdom Publications.

Wang, X. M., Hamza, M., Wu, T. X., & Dionne, R. A. (2009). Upregulation of IL-6, IL-8 and CCL2 gene expression after acute inflammation: Correlation to clinical pain. *Pain, 142*(3), 275-283.

Warden, D. (2006). Military TBI during the Iraq and Afghanistan wars. *J Head Trauma Rehabil, 21*(5), 398-402.

Warsi, A., LaValley, M. P., Wang, P. S., Avorn, J., & Solomon, D. H. (2003). Arthritis self-management education programs: a meta-analysis of the effect on pain and disability. *Arthritis Rheum, 48*(8), 2207-2213.

Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. (1993). The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. *Proceedings of the Annual Conference of the International Society for Traumatic Stress Studies*, Oct 25: San Antonio, Texas.

Weaver, B. (2002). *Chapter 3: Nonparametric Tests.* Retrieved from http://www.angelfire.com/wv/bwhomedir/notes/nonpar.pdf.

Weiner, R. (2002). *Pain Management: a practical guide for clinicians*. Florida: CRS Press.

Weinstein, S. M., Laux, L. F., Thornby, J. I., Lorimor, R. J., Hill, C. S., Jr., Thorpe, D. M., et al. (2000). Physicians' attitudes toward pain and the use of opioid analgesics: results of a survey from the Texas Cancer Pain Initiative. *South Med J, 93*(5), 479-487.

Williams, K. E., Chambless, D. L., & Ahrens, A.H. (1997). Are emotions frightening? An extension of the fear of fear concept. *Behaviour Research and Therapy, 35*, 239-248.

Wilson, K. G., Eriksson, M. Y., D'Eon, J. L., Mikail, S. F., & Emery, P. C. (2002). Major depression and insomnia in chronic pain. *Clin J Pain, 18*(2), 77-83.

Wilson, T., Eastman-Mueller, H., & Jung (2008) *Impact of Integrative Restoration (iRest) on College Students.* University of Missouri, Columbia, Missouri. Retrieved from http://www.irest.us/sites/default/files/Missouri_ACHA_Poster_0511.pdf

Wolfe, F., Hawley, D. J., & Wilson, K. (1996). The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol, 23*(8), 1407-1417.

World Health Organization (WHO). (1993). WHOQoL Study Protocol. Retrieved from http://www.who.int/mental_health/publications/whoqol/en/index.html

Zautra, A. J., Davis, M. C., Reich, J. W., Nicassario, P., Tennen, H., Finan, P., et al. (2008). Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J Consult Clin Psychol, 76*(3), 408-421.

Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The effects of brief mindfulness meditation training on experimentally induced pain perception. *J Pain, 11*(3), 199-209.

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. *Neurosci Lett, 520*(2), 165-173.

Zeidan, F., Johnson, S. K., Diamond, B. J., David, Z., & Goolkasian, P. (2010). Mindfulness meditation improves cognition: evidence of brief mental training. *Conscious Cogn, 19*(2), 597-605.

Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain mechanisms supporting the modulation of pain by mindfulness meditation. *J Neurosci, 31*(14), 5540-5548.

Zhou, D., Kusnecov, A. W., Shurin, M. R., DePaoli, M., & Rabin, B. S. (1993). Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. *Endocrinology, 133*(6), 2523-2530.

Zhukovsky, D. S., Gorowski, E., Hausdorff, J., Napolitano, B., & Lesser, M. (1995). Unmet analgesic needs in cancer patients. *J Pain Symptom Manage, 10*(2), 113-119.

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., et al. (2001). Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science, 293*(5528), 311-315.